Approaches to Asymmetric Synthesis. The Diastereoselective Alkylations of Chiral Propionamide Enolates

Thesis By

James Michael Takacs

In Partial Fulfillment of the Requirements
for the Degree of
Doctor of Philosophy

California Institute of Technology
Pasadena, California

1981

(Submitted January 19, 1981)

To My Parents

For Understanding

Know the Truth and the Truth

Shall Make You Free

ACKNOWLEDGEMENTS

I would like to thank Dave Evans for affording a stimulating research environment and the opportunity to learn science. His availability, his insights into chemistry, and the endless hours of enthusiastic discussions have made my tenure at Caltech an unforgettable period of growth as a scientist. I would also like to thank the other faculty at Caltech for their involvement during my stay.

I am indebted to all the members of the Evans group in many ways. While the chemistry has made the past four years exciting, the people have made it worthwhile. In particular I'd like to extend a special thanks to Terry and Sherri Taber, Ernst Vogel, Lew Mander, Sally Evans, Dave Baillargeon, Dave and Sally Hart, Ken Hurst, John Nelson, Mike Squillacote, and Larry McGee. Also, thank you Beckie for all you've done.

Finally, a special word of thanks to Dot Lloyd for typing this thesis.

ABSTRACT

Enantioselective propionate alkylation, as a method to control acyclic methyl-bearing stereocenters, is achieved *via* the diastereoselective alkylation of chiral propionamide enolates. The factors which control stereoselective enolization, diastereotopic differentiation of the enolate system, and selective cleavage of the chiral auxiliary are discussed. The application to the preparation of simple chiral carboxylic acids proceeds with the highest optical yields yet reported.

TABLE OF CONTENTS

	PAGE
LIST OF TABLES	xi
LIST OF FIGURES	xii
Diastereoselective Alkylation of Chiral Enolates	1
I. Introduction	2
II. Results and Discussion	7
A. Stereoselective Enolization	7
B. Preparative Results	20
C. Optimization of Dianion Alkylation Conditions	34
D. Alkylation of Boron-Ate Complexes	56
E. Reaction of O-Alkyl Derivatives	67
F. Other Substrates	72
III. Summary	84
IV. Experimental Section	85
General	85
General Acylation Procedure for the Preparation of Prolinol Derived Hydroxy-Amides	87
1-[(2S)-Hydroxymethylpyrrolid-1-yl]-propionic Acid (**15**)	87
1-[(2S)-Hydroxymethylpyrrolid-1-yl]-butanoic Acid (**16**)	88
1-[(2S)-Hydroxymethylpyrrolid-1-yl]-acetic Acid (**20**)	88

TABLE OF CONTENTS (continued) PAGE

General Procedure for the Enantioselective Alkylation of Chiral Hydroxy-Amide Derivatives 89

Preparation of Lithium Diisopropylamide (LDA) 89

Preparation of "Hexane-Free" LDA ... 89

Lithium Enolate Alkylation Conditions 89

Mixed Metal Enolate Alkylation Conditions 90

Standard Isolation Procedure 90

General Procedure for the Acidic Hydrolysis of Hydroxy-Amide Derivatives 91

(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2-methyl-1-butanoic Acid (28, Table 2, Entry A) 91

(R)-2-Methylbutanoic Acid (Table 2, Entry A) 92

(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2-methyl-1-hexanoic Acid (44, Table 2, Entry B) 93

(R)-2-Methylhexanoic Acid (Table 2, Entry B) 94

(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2-methyl-decanoic Acid (45, Table 2, Entry C) 94

(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2,4-dimethyl-1-pentanoic Acid (12, Table 2, Entry D) 95

(2R)-2,4-Dimethyl-1-pentanoic Acid (Table 2, Entry D) 96

TABLE OF CONTENTS (continued) PAGE

(2R,4S)-1-[(2S)-2-Hydroxymethyl-pyrrolid-1-yl]-5-benzyloxy-2,4-dimethyl-pentanoic Acid (47, Table 2, Entry E) 97

(2R,4S)-5-Benzyloxy-2,4-dimethylpentanoic Acid (48, Table 3, Entry E) 98

(2R,4R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-5-benzyloxy-2,4-dimethylpentanoic Acid (49, Table 2, Entry F) 98

(2R,4R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2,4-dimethylhept-6-enoic Acid (50, Table 2, Entry G) 99

(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2-methylpent-4-enoic Acid (51, Table 2, Entry H) 101

(R)-2-Methyl-1-pent-4-enoic Acid (Table 2, Entry H) 102

(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2-methyl-3-phenylpropionic Acid (52, Table 2, Entry I) 102

(R)-2-Methyl-3-phenylpropionic Acid (Table 2, Entry I) 104

(2S)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2-methyl-1-butanoic Acid (29, Table 2, Entry J) 104

(S)-2-Methylbutanoic Acid 105

1-[2-Hydroxymethylpyrrolid-1-yl]-4-methyl-pentanoic Acid (18) 105

(2S)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2,4-dimethylpentanoic Acid (46, Table 7, Entry 3) 106

Silylation of Amide Enolates 107

TABLE OF CONTENTS (continued) PAGE

Enolization With sec-Butyllithium 107

Enolization With LDA 107

General Procedure for the Observation of Lithium Enolates by ^{13}C NMR 108

1-[2-(Dihexylboroxymethyl)-pyrrolid-1-yl]-propionic Acid (22) 108

1-[2-(Dicyclohexylboroxymethyl)-pyrrolid-1-yl]-propionic Acid (24) 109

1-[2-(Dicyclopentylboroxymethyl)-pyrrolid-1-yl]-propionic Acid (25) 109

General Procedures for the Diastereoselective Alkylation of Borate Derivatives 110

Preparation of Potassium Hexamethyldisilylamide 110

Ate-Complex Alkylation Conditions 110

Oxidative Isolation Procedure 110

1-[2(S)-Methoxymethylpyrrolid-1-yl]-propionic Acid (30) 111

1-[(2S)-Methoxyethoxymethoxymethyl-pyrrolid-1-yl]-propionic Acid (32) 112

1-[2(S)-tert-Butyldimethylsilyloxymethylpyrrolid-1-yl]-propionic Acid (33) 113

1-[2-Dimethylhydroxymethylpyrrolid-1-yl]-propionic Acid (36) 113

1-[2-Dimethyl-(tert-butyldimethylsilyloxy)-methylpyrrolid-1-yl]-propionic Acid (37) 114

2-Hydroxymethyl-5-methylpyrrolidine 115

TABLE OF CONTENTS (continued) PAGE

1-[2-Hydroxymethyl-5-methylpyrrolid-1-yl]-propionic Acid (38, 40) 116

1-[2-(tert-Butyldimethylsiloxymethyl-5-methylpyrrolid-1-yl]-propionic Acid (39, 41) 116

V. References and Notes 118

APPENDIX I 127

APPENDIX II 153

LIST OF TABLES

		PAGE
Table 1.	Enolization Stereoselectivities	8
Table 2.	Diastereoselective Alkylations and Conversion to Optically Active Acids	26
Table 3.	Effect of Enolization Conditions on the Diastereoselectivity of Ethyl Iodide Alkylation	37
Table 4.	Effect of Solvent on Alkylation Diastereoselection	38
Table 5.	Effect of Electrophile Leaving Group on Alkylation Diastereoselection	40
Table 6.	Effect of Metal Counterion (17) on Alkylation Diastereoselection	42
Table 7.	Trends in Diastereoselection as a Function of Electrophile Structure	45
Table 8.	Alkylation of Amide Enol Borates With Ethyl Iodide	60
Table 9.	Alkylation of Alkoxy-Amide Derivatives	70
Table 10.	Alkylation of Methyl-Substituted Amides	78

LIST OF FIGURES

PAGE

Figure 1. Macrolide and Polyether Ionophoric Antibiotics 3

Figure 2. Requisite Free Energy Difference $\Delta\Delta G^{\ddagger}$ vs Product Selectivity for Diastereotopic Transition States 6

Figure 3. ^{13}C NMR of Pyrrolidylpropionamide Enolates 11

Figure 4. 500 MHz ^{1}H NMR Diethylpropionamide Enol Silyl Ethers 13

Figure 5. High Dilution IR Spectra of Hydroxy Amide 6 21

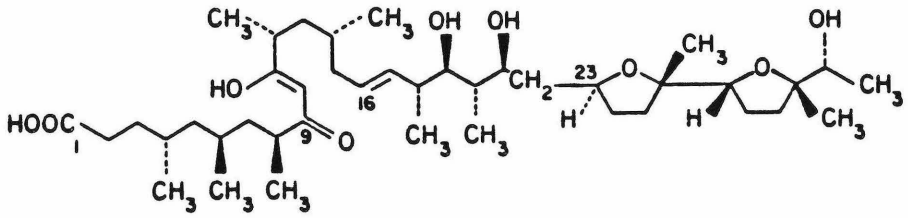
Figure 6. IR Evidence for N→O Acyl Transfer 33

Diastereoselective Alkylations of Chiral Propionamide Enolates

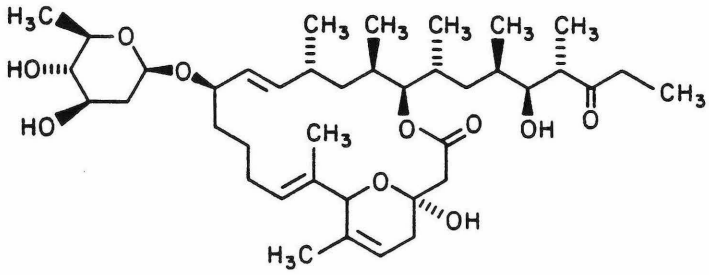
I. Introduction

The recognition of the often diverse biological activity of enantiomeric molecules and the need for control of relative stereochemistry between remote subunits in a convergent total synthesis have made techniques for the control of absolute configuration in the construction of asymmetric stereocenters a major objective in organic synthesis.[1] In light of the striking biological activity and beautiful molecular structure of the propionate derived macrolide and polyether ionophoric antibiotics[2] (Figure 1), we have focused our attention on the development of highly stereoselective carbon-carbon bond forming reactions. If available, induced enantioselection in the reactions of acyclic enolates would permit, in a manner independent of the acyclic stereochemical complexity present in the rest of the target structure, a very simple approach toward the construction of both the carbon framework and the absolute stereochemistry of a given stereocenter in a single chemical process.

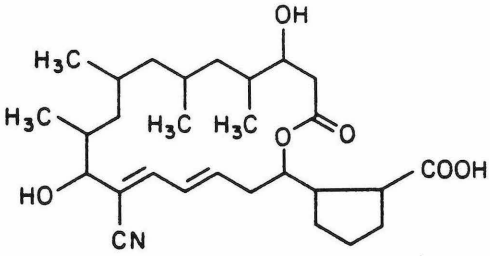
The problem of enantioselective alkylation or aldol condensation of an enolate can be approached in terms of the diastereoselective reaction of a chiral propionate enolate. This approach presents three independent problems



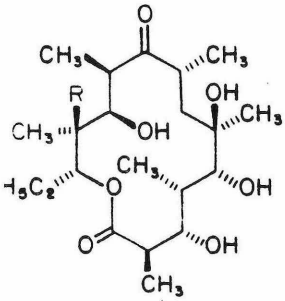
IONOMYCIN



VENTURICIDIN B



BORRELIDIN



A. R = OH
B: R = H

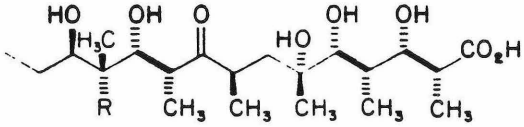
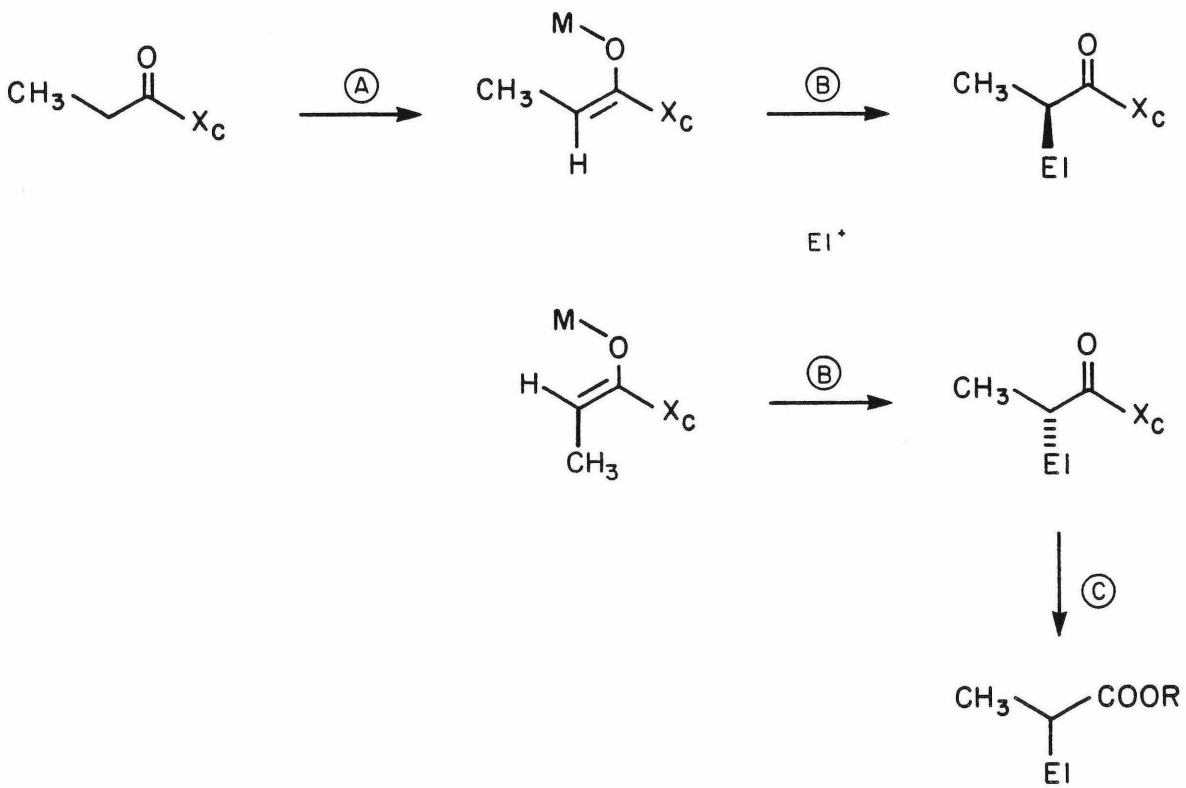


Figure 1

which contribute equally to the overall success of the asymmetric process. This requires as illustrated in Scheme I: a) High stereoselection in the enolization process to yield one enolate geometry; b) Orientation of the chirality in the auxiliary to provide high diastereotopic face discrimination of the enolate system toward electrophilic reagents; and c)Selective cleavage of the chiral auxiliary without loss of stereochemistry at the newly formed stereocenter. A viable

Scheme I



application of this approach to the total synthesis of molecules with numerous asymmetric centers necessitates coupling these three highly selective chemical processes to give an overall selection on the order of 95:5 for the construction of each individual stereocenter.

This is particularly challenging considering the energetics of competing similar reaction pathways. In a very simple approximation, as the desired ratio of reaction products increases from 50:50 to 99:1, the requisite difference in transition state free energies ($\Delta\Delta G^{\ddagger}$) for the competing pathways increases in an exponential manner. For example, a $\Delta\Delta G^{\ddagger}$ of about 1 kcal/mole, reflected in a 90:10 product distrubition, must be roughly doubled to achieve 99:1 product selection (Figure 2). Although the absolute magnitude of this difference is still quite small, it poses significant design problems for the engineering of high selectivity from bimolecular reactions where the reacting center is not constrained in a ring.

In spite of the fact that a good deal of work has been directed toward enantioselective alkylations, and a number of fundamental contributions toward understanding this process have been made, a practical solution to the problems discussed above has yet to be reported (Appendix I).[1,3-5] This paper describes, in full detail, our

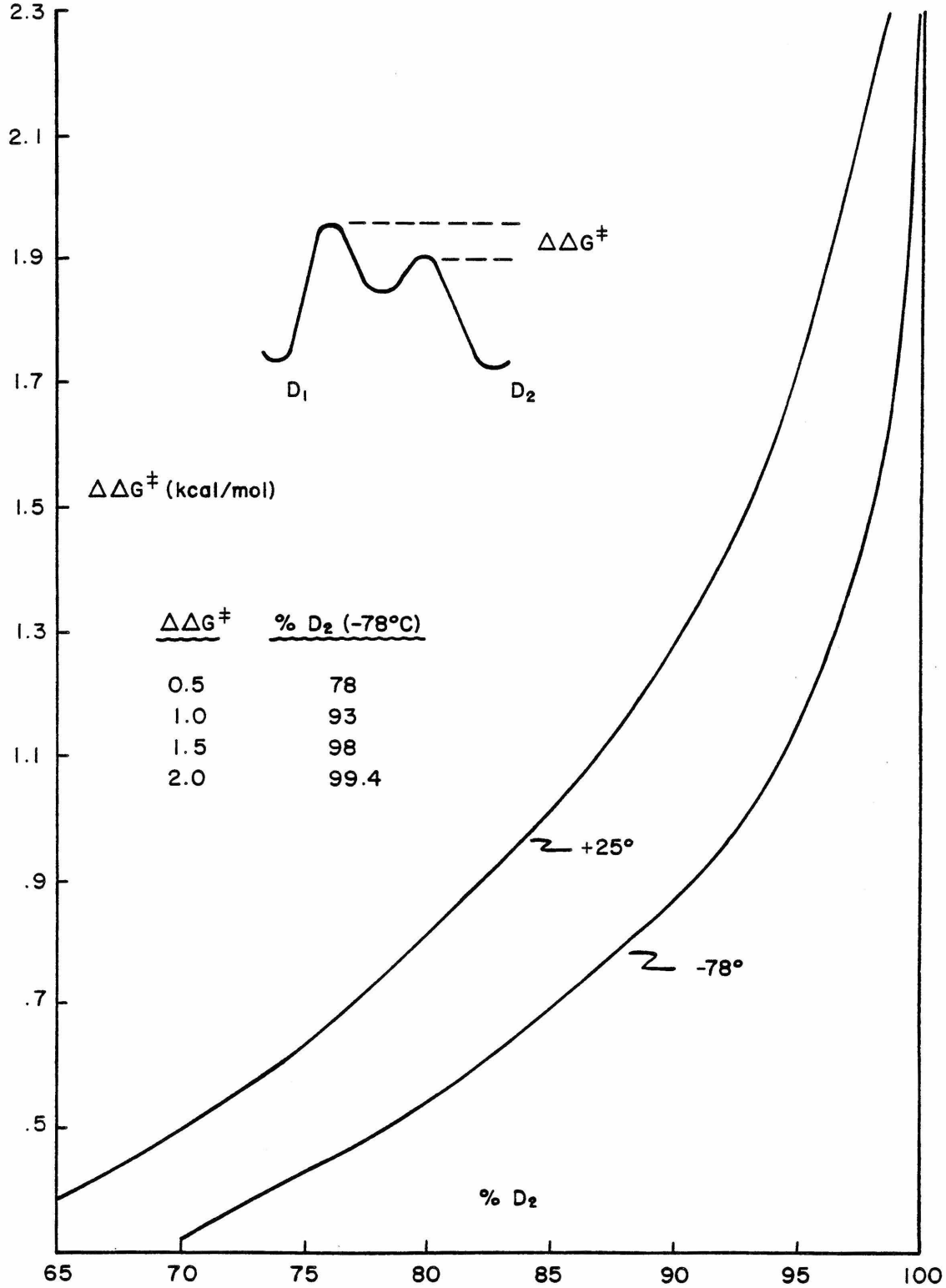

2.3
2.1
1.9
1.7
1.5
1.3
1.1
.9
.7
.5
ΔΔG‡ (kcal/mol)
ΔΔG‡
D1
D2
ΔΔG‡ % D2 (-78°C)
0.5 78
1.0 93
1.5 98
2.0 99.4
+25°
-78°
% D2
65
70
75
80
85
90
95
100

Figure 2

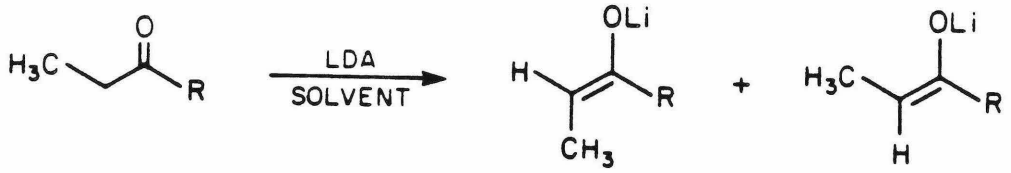
design notations and mechanistic understanding in the investigation of diastereoselective amide alkylation. The prolinol derived propionamide enolates represent a method for the construction of asymmetric methyl-bearing stereocenters in high enantiomeric purity.

II. Results and Discussion

A. Stereoselective Enolization. The nature of the strong base mediated enolization reaction has been of central interest as it correlates with stereochemical consequences of a number of rearrangements,[7] aldol,[8] and alkylation reactions.[9] Of these reaction classes, only the aldol process has so far shown promise for high reaction diastereoselection independent of enolate geometry.[10] In spite of its crucial role, stereoselective enolization is understood only in an empirical way.[8,11] Thus, as the acyl substituent R is made more sterically demanding from O-*tert*-butyl to *tert*-butyl, the percentage of cis enolate increases smoothly from 5 to >98% (Table 1, Entries A-D).[12,13]

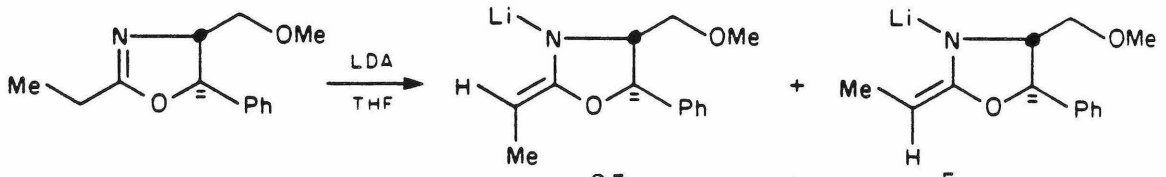
Recalling the overall goal in stereoselection, it was anticipated that dialkyl amides should show the same requisite high selectivity as propiophenone (>98:2,

Table 1.

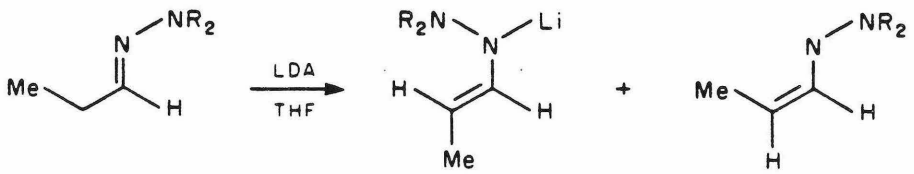


Entry	R	Solvent	Trans	:	Cis
A	O-t-C_4H_9	THF	95	:	5
B	C_2H_5	THF	70	:	30
C	i-C_3H_7	THF	40	:	60
D	t-C_4H_9	THF	<2	:	98
E	C_6H_5	THF	<2	:	98
F	O-t-C_4H_9	HMPA-THF	23	:	77
G	C_2H_5	HMPA-THF	5	:	95

[a]Analysis of the O-silyl derivatives.

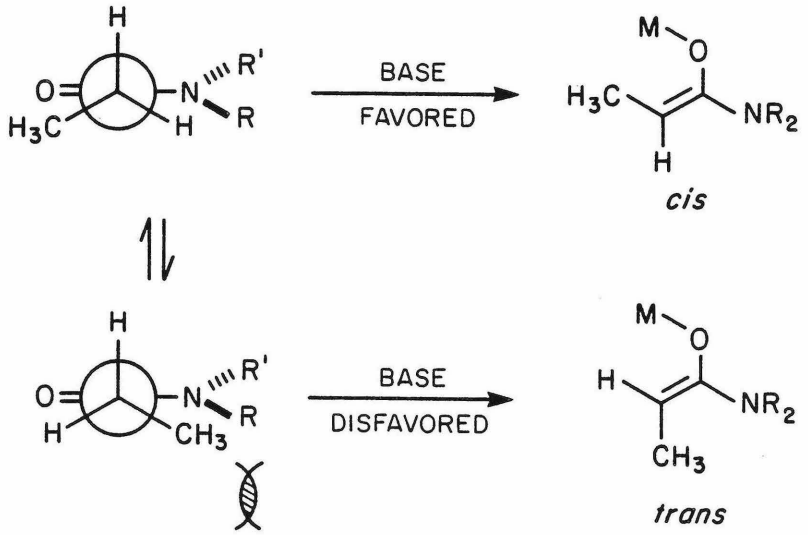


95 : 5



>95 : 5

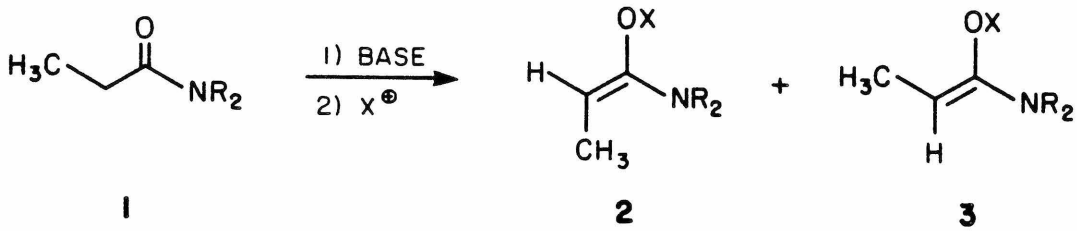
Entry E), perhaps due to a developing $A_{1,3}$ strain disfavoring the T.S. leading to the trans enolate (eq 1). Two conflicting reports have appeared with regard to this question (eq 2). Heathcock[11] reported the silylation of diisopropyl propionamide to give an 19:81 mixture (2a, 4.05 ppm; 3a, 4.38 ppm) by integration of the vinyl



(1)

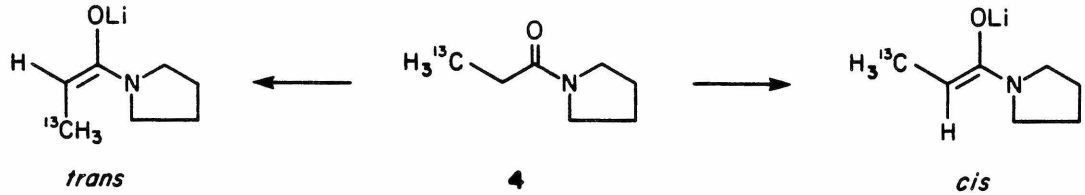
proton signals in the NMR spectrum. In contrast, Rathke[14] reported a single vinyl resonance for 3b at 3.4 ppm. For the corresponding dimethyl amide, he reported no difference in chemical shift of the vinyl proton for either the trimethyl silyl (TMS) or tert-butyldimethylsilyl (TBS) ether.

In studies directed toward resolving this question, we have examined, using both direct observation and silylation, the enolization of simple achiral propion-



a, R = *i*-Pr X = TBS
b, R = *i*-Pr X = TMS
c, R = Et X = TBS

amides as models for the prolinol derived systems. Deprotonation of ^{13}C-labeled pyrollidylamide 4 (eq 3) with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) gave rise to a single discernable methyl resonance in the ^{13}C NMR spectrum (11.7 ppm, Figure 3). Treatment with LDA in 10% hexamethylphoramide (HMPA) in THF, conditions



which generally favor increased formation of the cis enolate (Table 1, Entries F, G),[7,11] affords the same single methyl resonance, now at 12.3 ppm due to solvation effects. Attempts to generate an authentic mixture of enolates under equilibrating conditions with excess propionamide or potassium hexamethyldisilylazide

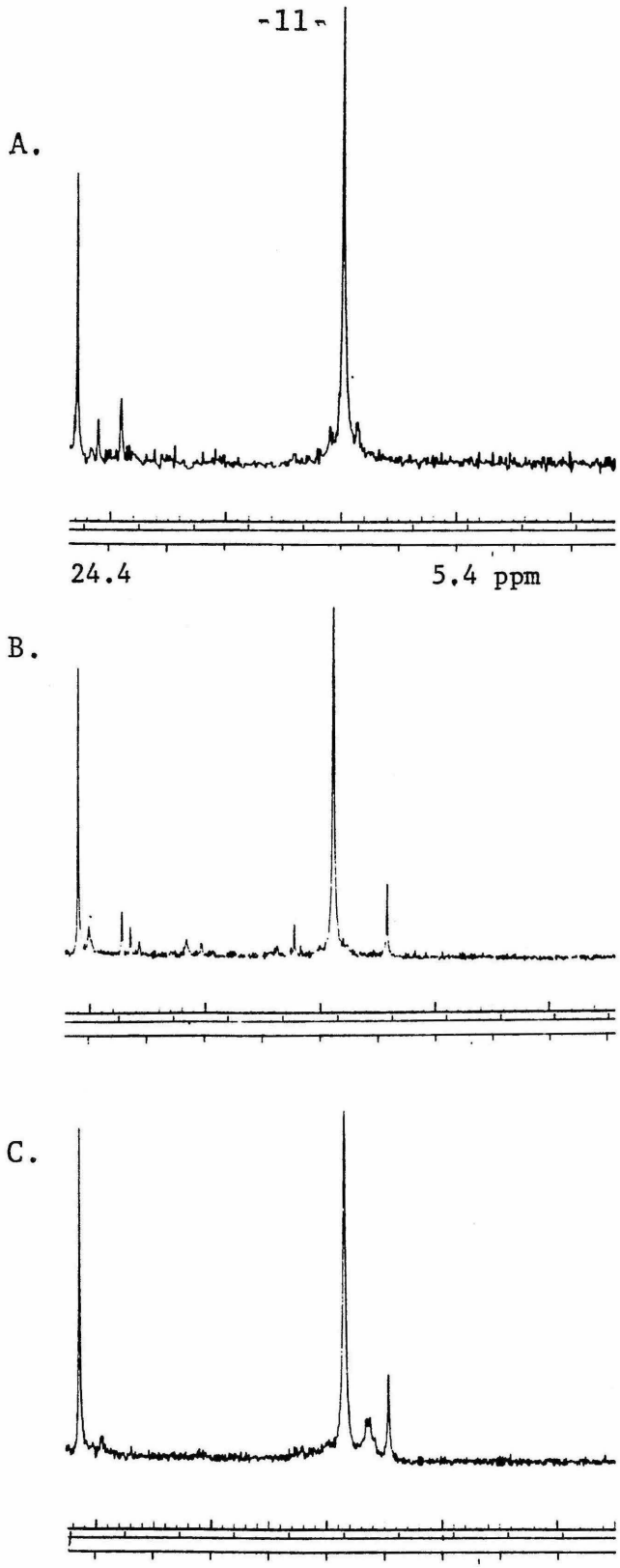


Figure 3. ^{13}C NMR (THF) of pyrollidylpropionamide enolates. Base employed was: a) LDA; b) LDA/HMPA; c) sec-BuLi.

(HMDS) as the base, failed to provide unambiguous evidence for a second enolate. Enolization using sec-butyllithium, under conditions which show the lowest enolate geometry selectivity with Meyer's chiral oxazolines,[9] gives rise to a minor ^{13}C-resonance in a region consistent with the second enolate isomer (10.4 ppm, Figure 3).

Treatment of diethylpropionamide (1c) with LDA or sec-butyllithium in THF followed by addition of tert-butyldimethylsilyl chloride yielded, in addition to the minor carbon-silylated by-product which was virtually eliminated by addition of HMPA prior to silylation, the TBS-enol ether (eq 2). The 90 MHz ^{1}H NMR spectrum showed a single downfield quartet (3.52 ppm) due to the vinyl proton. Examination of these products by ^{1}H NMR at 500 MHz revealed, in the case of s-butyllithium enolization, two overlapping quartets (3.539 and 3.534 ppm) for the vinyl protons and two overlapping doublets (1.451 and 1.445 ppm) for the vinyl methyl protons of TBS-ethers 2c and 3c. The product from LDA enolization exhibited a single set of signals (Figure 4; a,b). The overlapping signals are indeed surprising in light of the reported chemical shift of 3.90 ppm for the vinyl proton of the TMS-enol ether derived from N-methyl-δ-valerolactam, which is constrained to be trans.[14] This may reflect

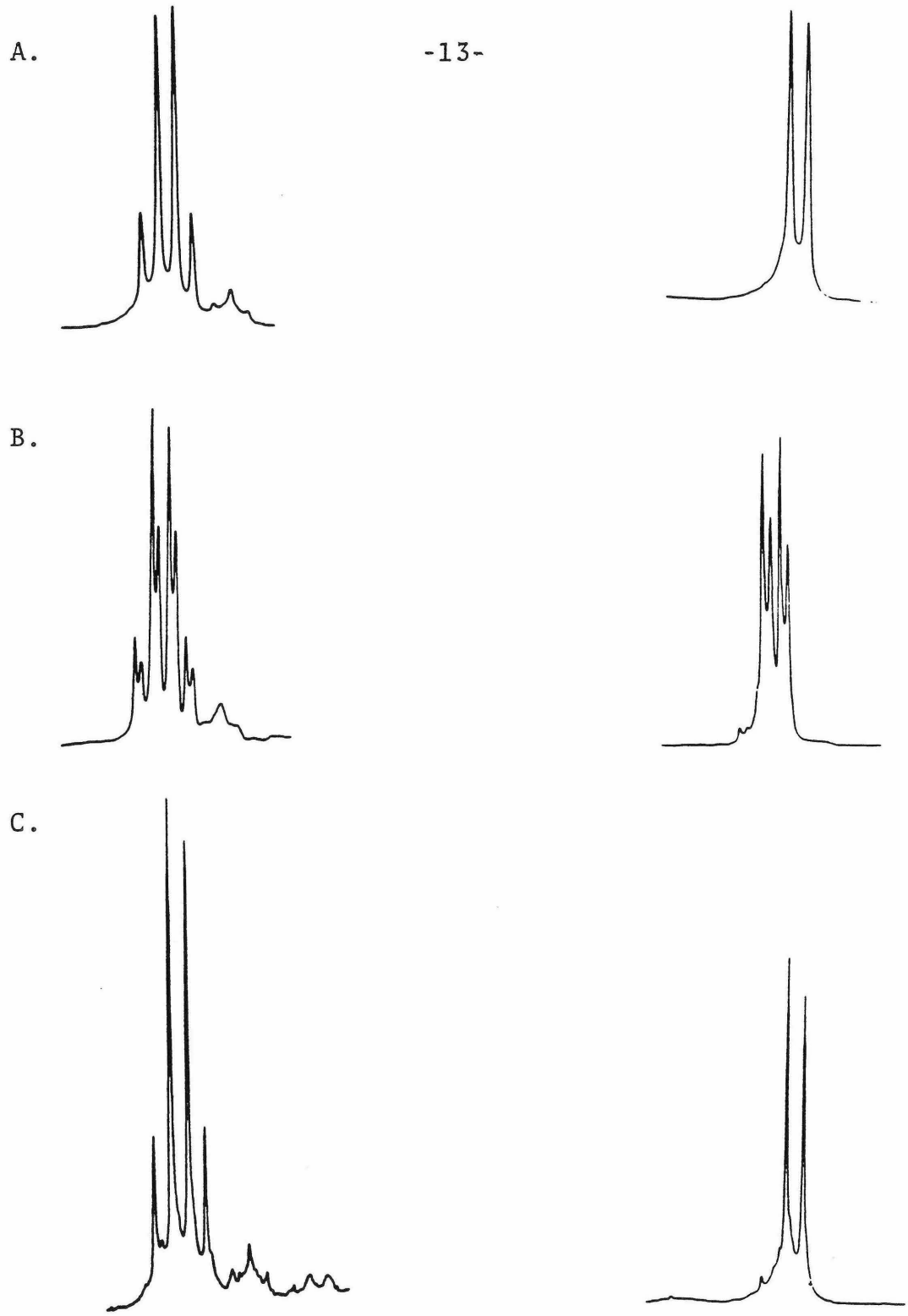


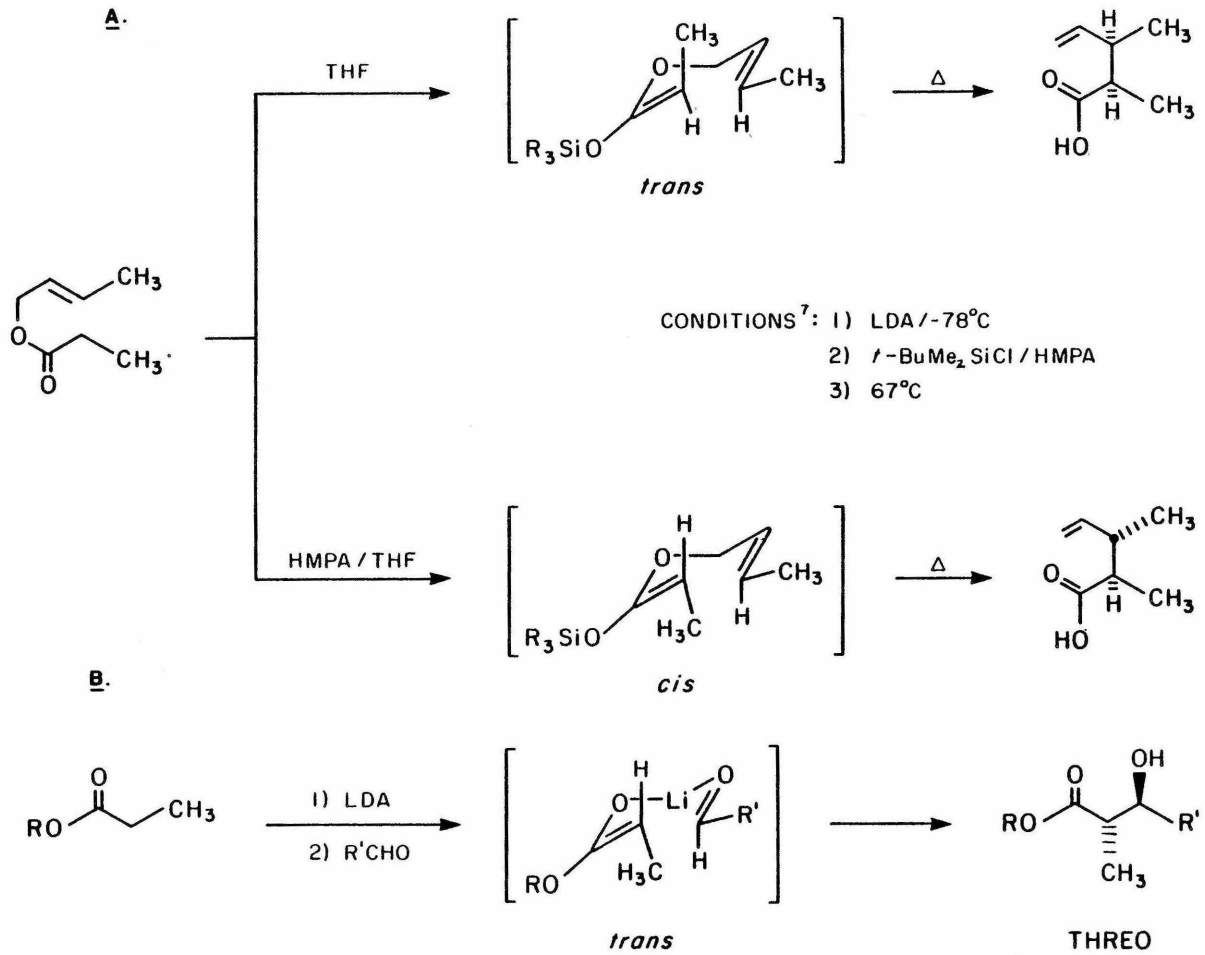
Figure 4. 500 MHz ^{1}H NMR (CCl_4) of the vinyl quartet (10 Hz/cm) and methyl doublet of silyl enol ethers 2c and 3c. A. Enolization with LDA. B. Enolization with sec-butyllithium. C. Equilibration of mixture B with pyridinium tosylate.

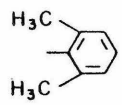
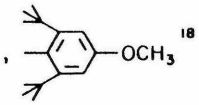
the different conformations available to the acyclic system and points out the potential danger in invoking stereochemical assignments purely on the basis of spectroscopic analogy. Attempts to prepare an authentic mixture of silyl enol ethers by addition of tert-butyldimethylsilanol across 1-diethylaminopropyne gave only the disilyloxane resulting from dehydration.[15]

It is important to note that in some cases not only the sense, but also the degree of asymmetric induction is critically dependent on which enolate geometry is obtained.[9] In our case, determining the correct assignment of cis or trans amide enolate geometry will be crucial to a mechanistic understanding of diastereoselective alkylation in the chiral enolates. Previous assignments of enolate geometry have been made by: 1) Spectroscopic analogy to aldehyde and endocyclic enol ethers; 2) Inference from the stereochemical results of aldol condensations and sigmatropic rearrangements assuming a pseudo-chair pericyclic transition state; and 3) Thermodynamic considerations.

As illustrated in Scheme II, Ireland[7] reported the enolate Claisen rearrangement to have strikingly different stereochemical results dependent on enolization conditions. Assuming a chair-like transition state, the enolate geometry formed in the presence of

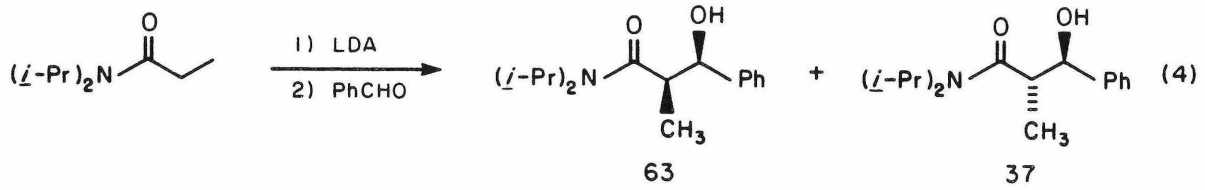
Scheme II



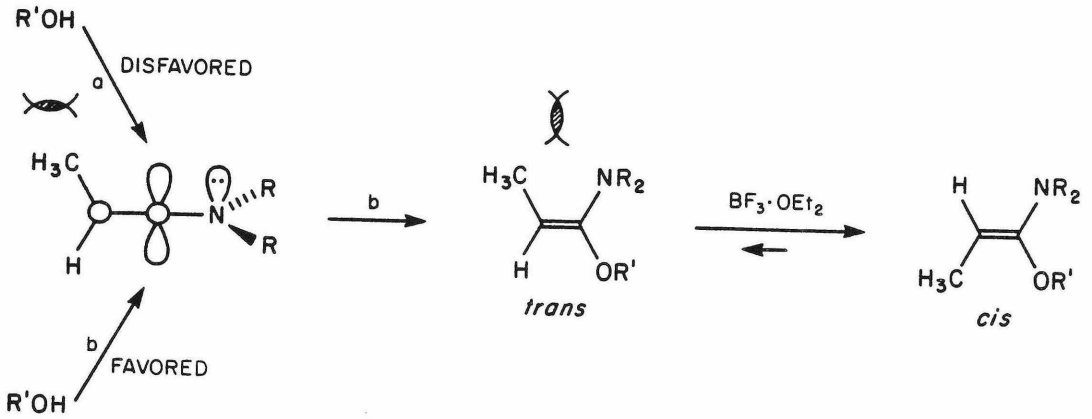
R = $-CH_2OCH_3$, $-CH_2OCH_2CH_2OCH_3$[17],  ,  [18]

HMPA must have been cis. The same enolate geometry was obtained under the described conditions from 3-pentanone, which had been assigned earlier by House (Table 1).[16] Recent work by Meyers[17] and Heathcock[18] provides corroborating evidence for the claims of enolate geometry by an independent test. Assuming now aldol diastereoselection to reflect the steric constraints of a chair-like transition state, the observation of threo diastereoselection in the aldol condensation of certain esters implicates the intermediacy of the expected trans enolate (Scheme II).

In the case of amides, little substantiated literature data is available on the stereochemistry of strong base enolization. Predominantly cis enolate geometry has been assigned in analogy to propiophenone; the subsequent aldol condensation is in this case non-selective (eq 4).[11] Studies on the Claisen rearrangement

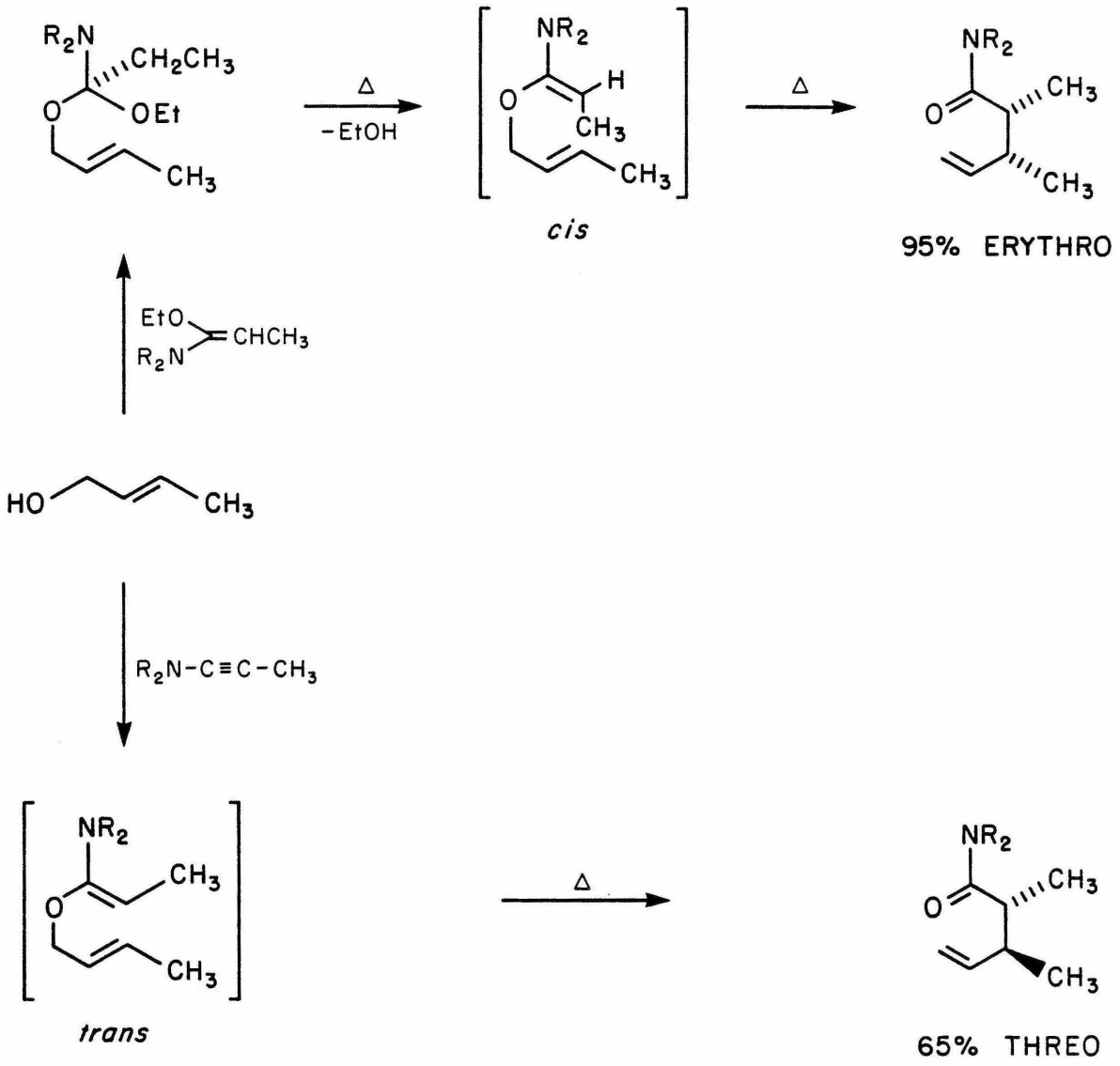


suggest the cis enolate derivative to be at least thermodynamically favored. Assuming a chair-like transition state, rearrangement from an amide acetal to give 95% erythro product must proceed through a cis ketene acetal (Scheme III).[19] Direct conversion of allylic alcohol to ketene acetal by reaction with an ynamine, however, proceeds via a different course (eq 5). Addition of alcohol to a dilute refluxing solution of ynamine traps the apparently kinetic trans ketene acetal, resulting from net cis-1,2-addition across the triple bond, affording predominantly the threo product (Scheme III). In the presence of higher concentration of alcohol or acid catalysis, rearrangement via the thermodynamic cis acetal is observed and the erythro product is almost exclusively obtained (eq 5).[20]



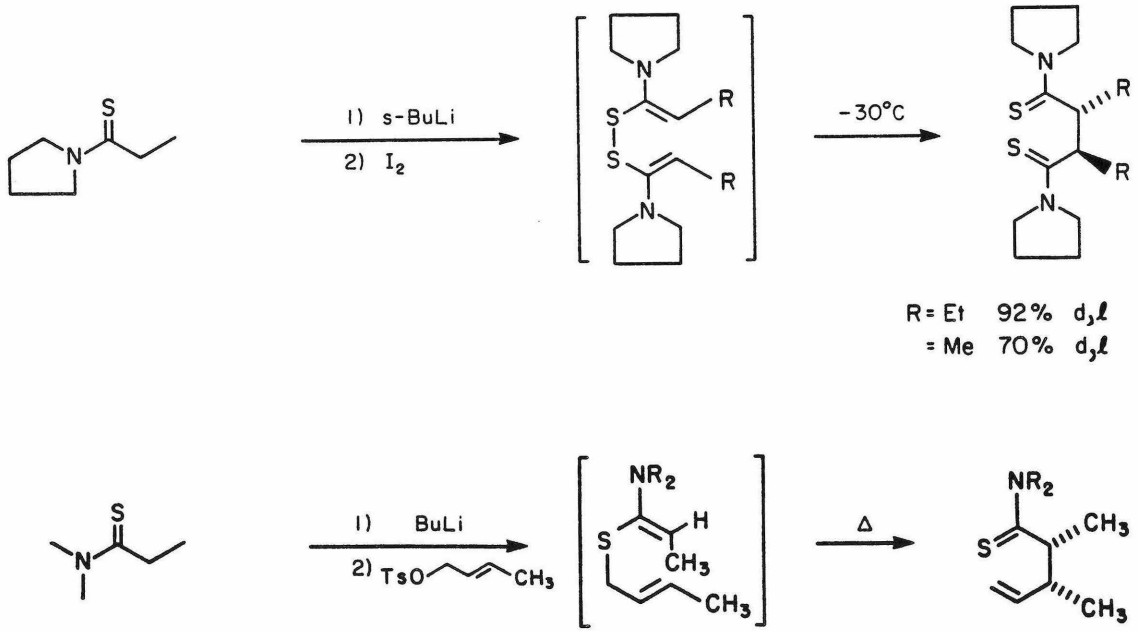
(5)

Scheme III


R2N
CH2CH3
OEt
CH3
Δ
-EtOH
NR2
H
CH3
cis
95% ERYTHRO
EtO
R2N
CHCH3
HO
R2N-C≡C-CH3
trans
65% THREO

Enolization of thioamides under a variety of kinetic conditions has been the subject of conflicting reports by Yoshida.[21,22] Evidence for both cis and trans thioether intermediates in [3,3]-rearrangements has been presented (Scheme IV). Again, mild acid or heating is claimed to equilibrate the olefin geometry to predominantly cis.[21]

Scheme IV

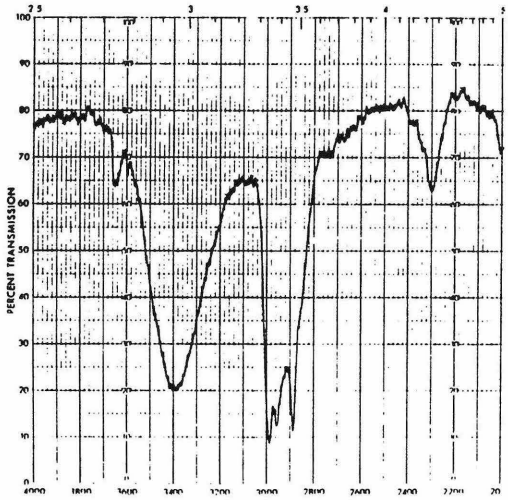


The assignment of enolate geometry, obtained in our amide deprotonation studies discribed above, was made as follows. Treatment of the presumed mixture of enol ethers 2c and 3c from the sec-butyllithium reaction with a catalytic amount of pyridinium tosylate shows an apparent equilibration of the minor component to the same enol ether produced by LDA deprotonation (Figure 4; C). This permits on the basis of thermodynamic considerations (eq 5) and in analogy to the work described above, assignment of the cis stereochemistry to amide enolization.

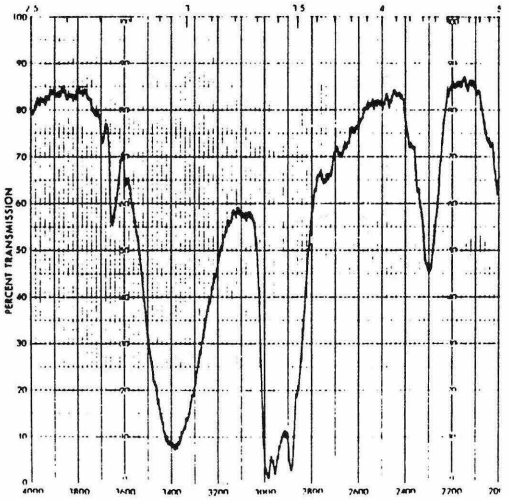
B. Preparative Results. With a reasonable confirmation of both the sense and degree of stereoselection in the enolization step of the asymmetric alkylation problem, we turned our attention to developing a practical chiral propionamide which would show high diastereoface discrimination. Toward that end we have examined the alkylation of prolinol derived amides.[5a] The hygroscopic hydroxy-amides 6 were conveniently prepared by acylation of (ℓ)-prolinol with the appropriate anhydride (eq 6, 65°C, neat, 10 min, 90%) and were purified and dried by bulb-to-bulb distillation under reduced pressure just prior to use. The amino alcohol is available in high optical purity from commercial sources or from borane reduction of the proline-BF_3 complex.[23]

High dilution infrared studies and ^{13}C NMR indicated amide 6 existed in primarily the hydrogen-bonded amide rotomer 6-syn (Figure 5). These important observations (eq 7)

A.



B.



C.

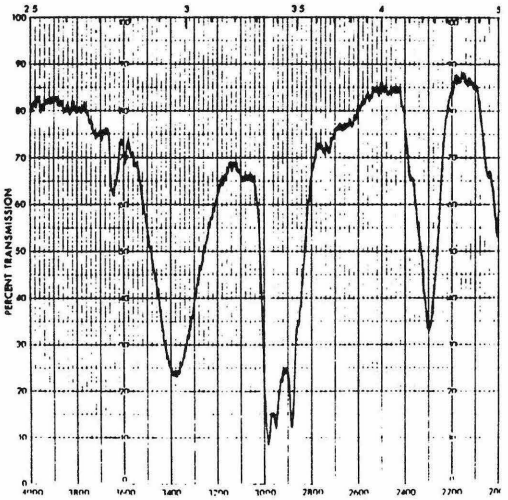
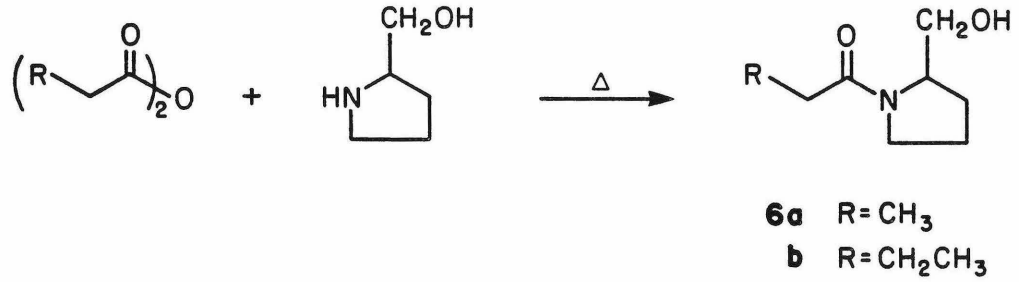
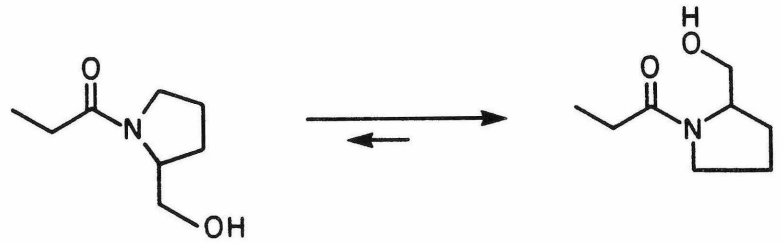


Figure 5. High dilution IR spectra of hydroxyamide 6 (eq 7). A) c = 0.1 M, ℓ = 2.0 mm. B) c = 0.066 M, ℓ = 3.0 mm. C) c = 0.02 M, ℓ = 4.0 mm.



(6)

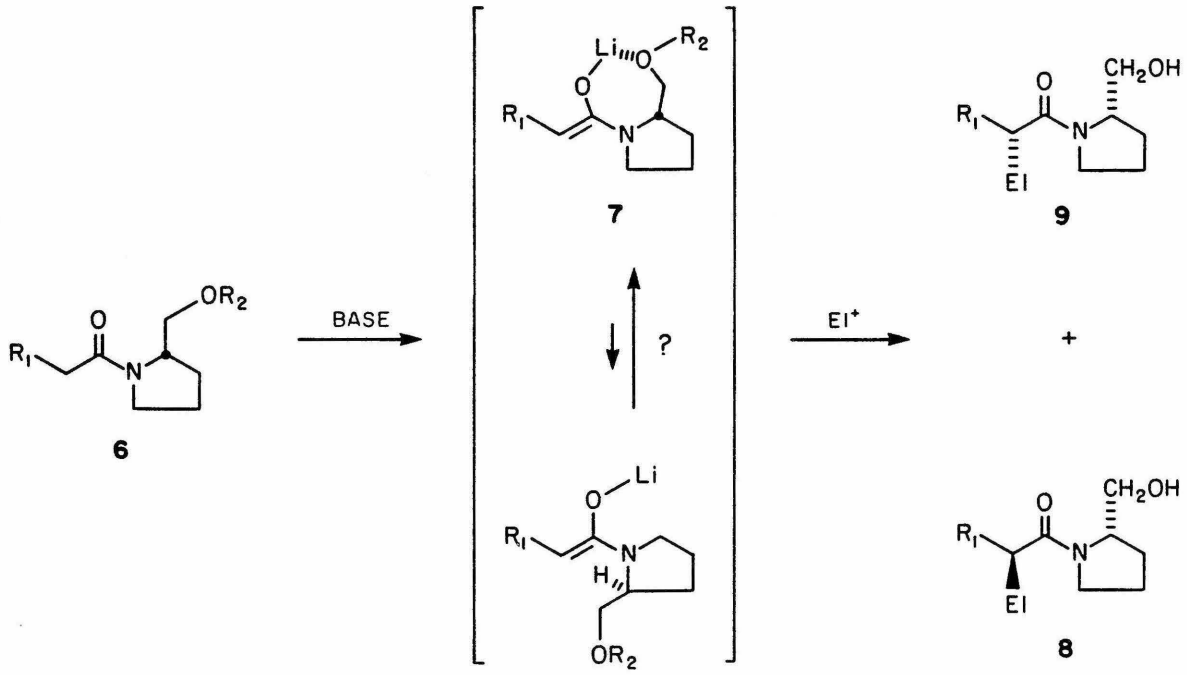


(7)

6-ANTI **6**-SYN

provided encouragement that the pendant hydroxyl could be used via a seven-membered ring chelate 7 to orient the relatively rigid pyrrolidine ring of the chiral auxiliary for a distinct diastereotopic facial bias. The hydroxyl moiety provides a unique degree of flexibility in the design and exploitation of this chelation control concept for restricting transition state geometry in a conformationally mobile system (Scheme V).[24a,b] This approach to the control of acyclic stereochemistry issues a striking alternative to the use of preformed carbo- or in some cases heterocycles to direct the desired bond construction followed in subsequent steps by the destruction of that ring.[24c,d] Thus the initial criteria for high diastereo-

Scheme V

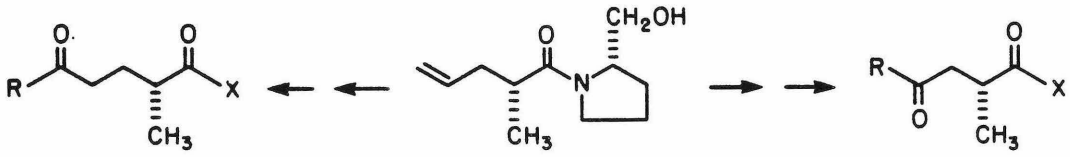

OR2
O
R1
N
6
BASE
Li
O
R2
O
R1
N
7
?
Li
O
R1
N
H
OR2
EI+
CH2OH
O
R1
N
EI
9
+
CH2OH
O
R1
N
EI
8

selection represent a fine balance in delicate equilibria controlled by: 1) The use of prolinol derived amides to ensure one enolate geometry; 2) The use of chelation to limit rotation about the C-N bond; 3) The reaction of that single rotomer through primarily one conformation; and 4) The effective bias of that conformation to induce reaction from only one side of the enolate system.

Deprotonation of rigorously dried amide derivatives 6 proceeds smoothly with LDA in THF (20 min) at room temperature or below (-78°C). For convenience, ambient temperatures are most commonly employed. This is in contrast to published reports[5a,c] of extended reaction times and substantial excesses of strong base, which may reflect the hygroscopic nature of these amides. Alkylation proceeds with a variety of alkyl halides under conditions optimized for each pair of substrates. In all experiments, the primary means of diastereomer analysis (8:9) was carried out by gas chromatographic separation. This analytical method proved to be invaluable in determining, typically with a high degree of precision, the efficiency of asymmetric induction during enolate alkylation. This made possible the systematic investigation and optimization of a variety of subtle effects which can contribute, often

unpredictably, to the overall diastereoselection. These diastereomer ratios and the optical purity of the chiral carboxylic acids derived via hydrolysis, vide infra, show good agreement as to the enantiomeric purity of the newly formed center.

The preparation of simple chiral carboxamides which may serve as useful subunits for further elaboration in asymmetric synthesis, are summarized in Table 2. The R-configuration is obtained at the newly formed center by alkylation of the propionamide derived from (S)-prolinol. Of particular note are the selectivities (8:9, >25:1) observed in Entries D-H. The γ,δ-unsaturated amide (Entry H) should find utility as a precursor to a variety of further oxidized species (eq 8). The success of



(8)

the iso-butyl type electrophiles (Table 2, Entries D-G) carry obvious implications for the construction of chiral 1,3-methyl-substituted stereocenters prevalent in macrolide and ionophoric antibiotics (Figure 1). For example, the partial retrosynthetic analysis of a

Table 2. Diastereoselective Alkylations and Conversion Optically Active Carboxylic Acids (Scheme V).

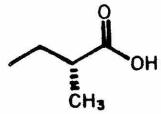
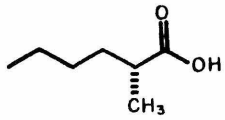
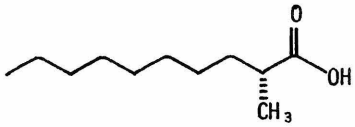
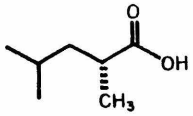
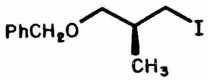
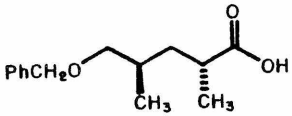
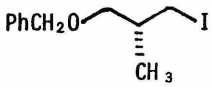
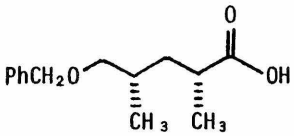
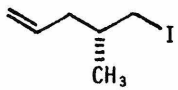
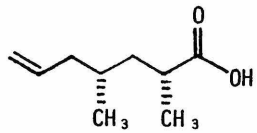
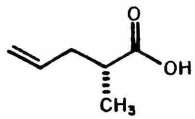
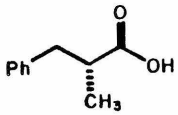
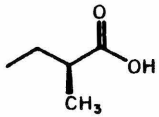
Entry	Amide	Electrophile[a]	Ratio 8:9[b]	(% Yield)	Hydrolysis Product[c]	(% Yield)	$[\alpha]_D$[d]	(lit.)	Overall Yield	(config.)
A	6a	CH_3CH_2I	92:8	(98)		(84)	-15.95°	(19.6°)[e]	82	(R)
B	6a	n-C_4H_9I	94:6	(99)		(78)	-16.71°	(18.7°)[f]	77	(R)
C	6a	n-$C_8H_{17}I$	94:6	(78)						(R)
D	6a	i-C_4H_9I	97:3	(84)		(96)	-21.86° C=5.39	(19.4°)[g] (C=5.23, Et_2O)	81	(R)
E	6a		97:3	(59)		(91)			54	
F	6a		98:2	(78)						(R)

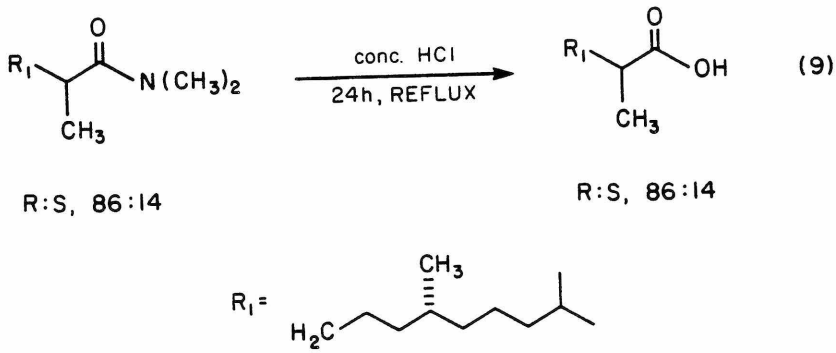
Table 2. Continued

Entry	Amide	Electrophile[a]	Ratio 8:9[b] (% Yield)	Hydrolysis Product[c]	(% Yield)	$[\alpha]_D$[d]	(lit.)	Overall Yield	(config.)
G	6a		97:3 (52)						
H	6a		96:4 (98)		(89)	-7.62°	(8.24°)[h]	87	(R)
I	6a	$PhCH_2Br$	88:12 (75)		(92)	-18.89°	(-25.4°)[i]	69	(R)
J	6b	CH_3I	94:6 (98)		(96)	+17.03°	(19.6°)[e]	95	(S)

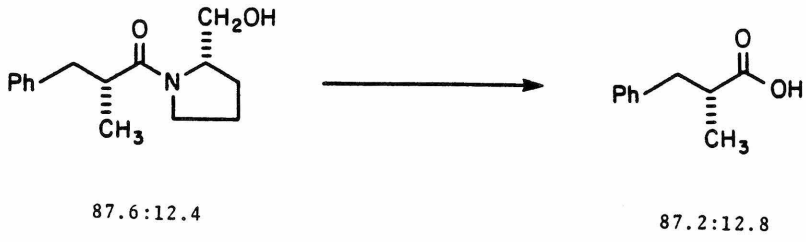
[a]All reactions run in THF. Entries A, B, D, E, H, I, J employ the dilithio anion. Entries C, F, G employ the mixed metal enolate. Entries A, B add electrophile at 25°C. Entries C-J add 2 equiv of HMPA followed by cooling to -78°C for the mixed metal or -100°C for the dilithio enolates and addition of electrophile. Entry I add electrophile at -78°C. [b]All diastereomer ratios determined by integration of the peak areas on gas chromatography. [c]Hydrolysis performed in refluxing 1 N HCl for 2-3 h followed by cooling and addition of base. [d]All rotations reported neat unless otherwise noted. [e]A. Kjaer and S. E. Hansen, Acta Chem. Scand., 11, 898 (1957). [f]P. A. Levene and R. E. Marker, J. Biol. Chem., 98, 1 (1932). [g]P. A. Levene and L. W. Bass, J. Biol. Chem., 70, 211 (1926). [h]G. I. Fray and N. Polgar, J. Chem. Soc., 2036 (1956). [i]G. Helmchen, et al., Angew. Chem. Int. Ed., 18, 63 (1979).

number of complex natural products in Scheme VI points out the utility of the bond construction exemplified by Entries D and E.

The utility of chiral amides depends on their facile conversion to other carbonyl derivatives. Reports of amide hydrolysis without appreciable epimerization suggested prolinol derived amides would find general utility (eqs 9-10).[25] The results summarized in Table



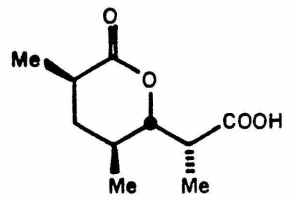
(9)



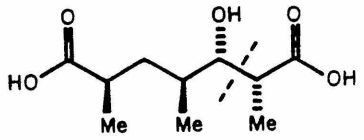
(10)

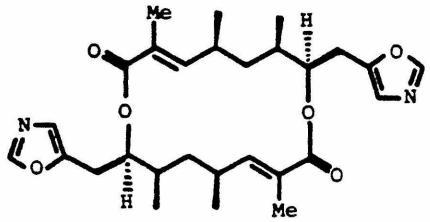
2 confirm this suggestion. For example, starting with a diastereomer ratio (8:9) of 87.6:12.4 (Entry I, eq 10) hydrolysis (1N HCl, 100°C, 2 h) yields the corresponding benzyl propionic acid (92%) as an 87.2:12.8 mixture of enantiomers judged by optical rotation. The butenoic acid prepared in Entry H has been further analyzed by

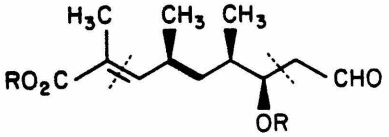
Scheme VI

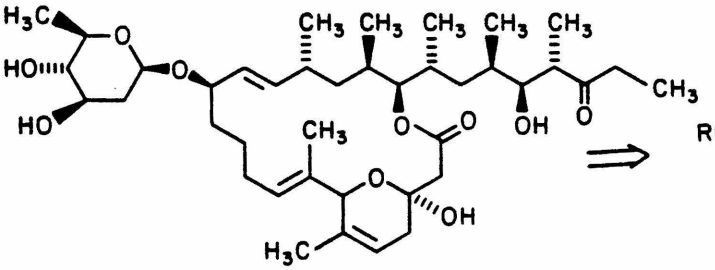


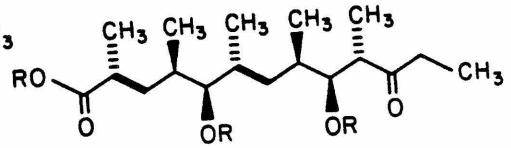
Prelog-Djerassi Lactone









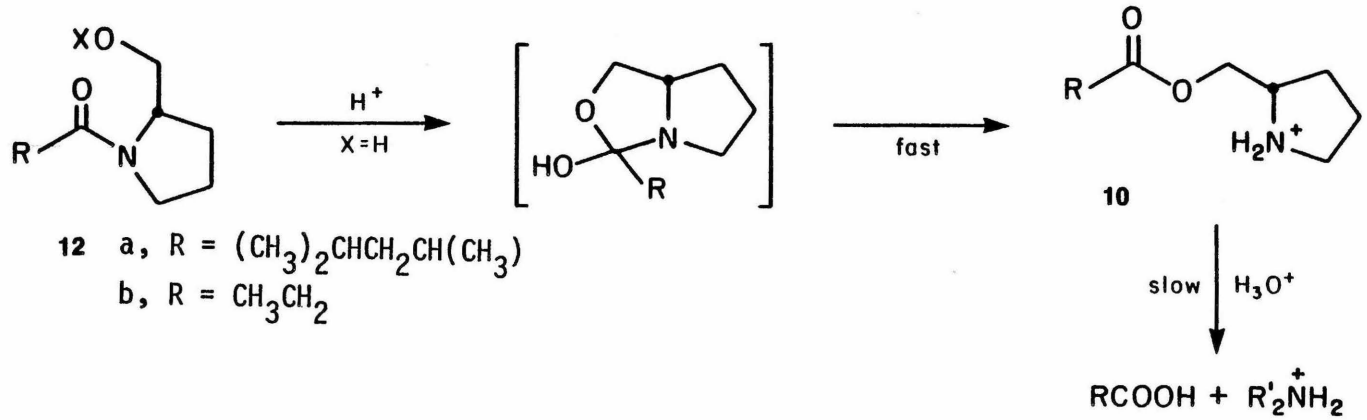


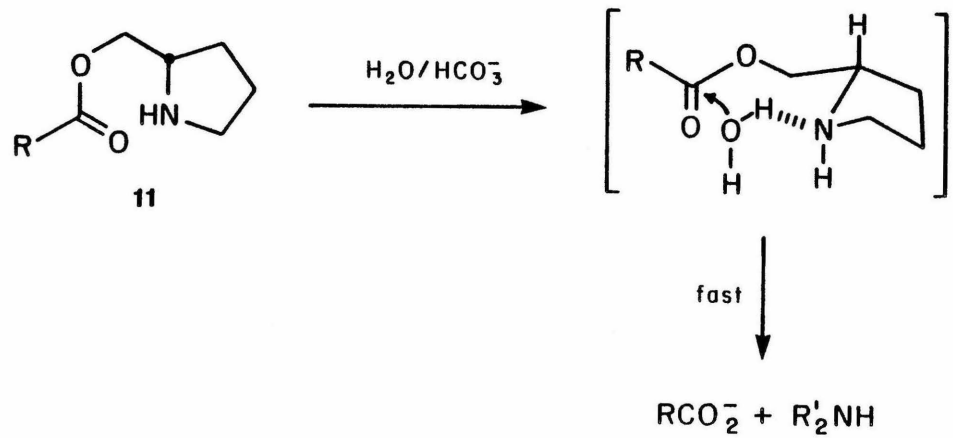
VENTURICIDIN B

conversion to the alkyl iodide and subsequent alkylation. Analysis of the new diastereomeric mixture at C_4, by gas chromatography (Entry G) places an upper limit of $<2\%$ loss in stereochemistry due to either optical impurity in the starting amide or epimerization during hydrolysis, reduction and conversion to the iodide. The preparation of optically active 2-methyl-hexanoic acid permits direct comparison of this work to existing asymmetric alkylations. Butyl iodide alkylation of a chiral oxazoline yields acid with a rotation, $[\alpha]_D$, of +14.1°.[5h] Reaction of the magnesium enolate of an ephedrine derived amide[5c] gave -14.5° while the present preparation shows a significantly higher rotation of -16.7° (Entry B). Of the common chiral propionate substrates for asymmetric alkylation, the prolinol-derived amides are of the lowest molecular weight giving them a very practical edge in ease of handling and application.

It was anticipated that the hydroxyl moiety, in addition to enolate chelation, would perform a crucial role to facilitate amide hydrolysis <u>via</u> acid catalyzed N → O acyl transfer (Scheme VII).[26] Analysis of the reaction products after refluxing amide **12** in 1N HCl (2 h) revealed only minor amounts of carboxylic acid or starting amide. Careful neutralization followed by rapid extraction yields the major component which shows

Scheme VII


XO
O
R
N
12 a, R = $(CH_3)_2CHCH_2CH(CH_3)$
b, R = CH_3CH_2
H^+
X=H
O
HO
N
R
fast
O
R
O
H_2N^+
10
slow
H_3O^+
RCOOH + $R'_2\overset{+}{N}H_2$


O
HN
R
O
11
H_2O/HCO_3^-
R
O
O
H
O
H
N
H
H
fast
RCO_2^- + R'_2NH

replacement of the amide carbonyl absorbance (1600 cm^{-1}) with a new band at 1720 cm^{-1} consistent with amino ester 11. Upon standing at room temperature, 11 slowly reverts back to the starting prolinol amide by O → N acyl transfer (Figure 6). The rate of acyl transfer is markedly dependent on amide structure. The acetyl derivative 6 (R_1 = H), unlike the more substituted amides, shows an apparent amide → ester equilibration upon standing. Basification of the crude acidic hydrolysis mixture followed by reacidification gives a good yield of carboxylic acid, perhaps by an internally assisted base catalyzed hydrolysis of 11 (Scheme VII).[27]

Competitive hydrolysis experiments demonstrate a significant rate acceleration due to the hydroxyl substituent. Hydroxyamide 13, in direct contrast to the α-methyl analogue (Table 2, Entry H), has been the least successful hydrolysis substrate both in terms of the slowest rate and a major side reaction to give γ-lactone *via* olefin hydration. In spite of this, hydroxyamide 13 shows at least a ten-fold initial rate enhancement relative to methoxyamide 14 where acyl transfer has been precluded (eq 11).

A.

B.

C.

D.

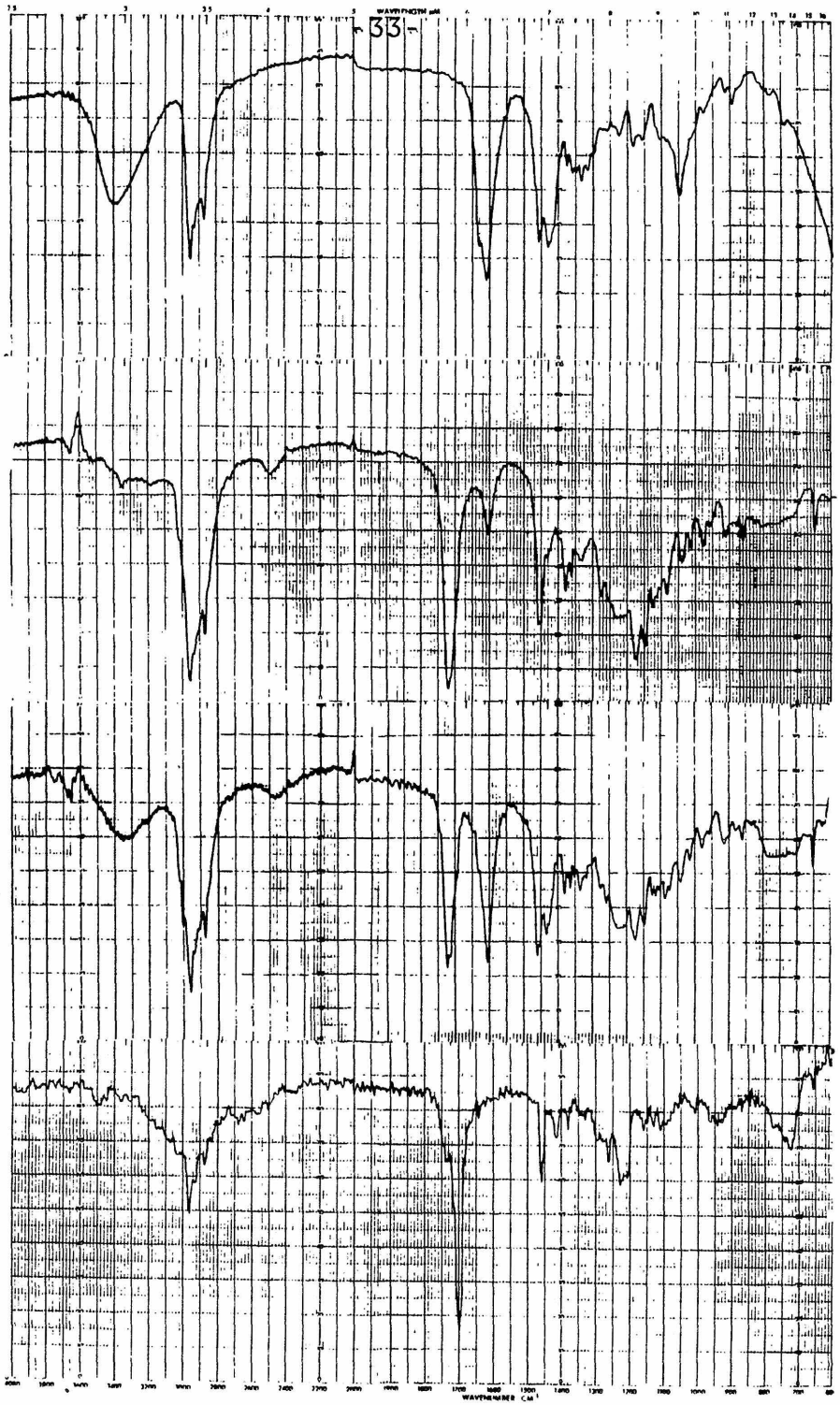
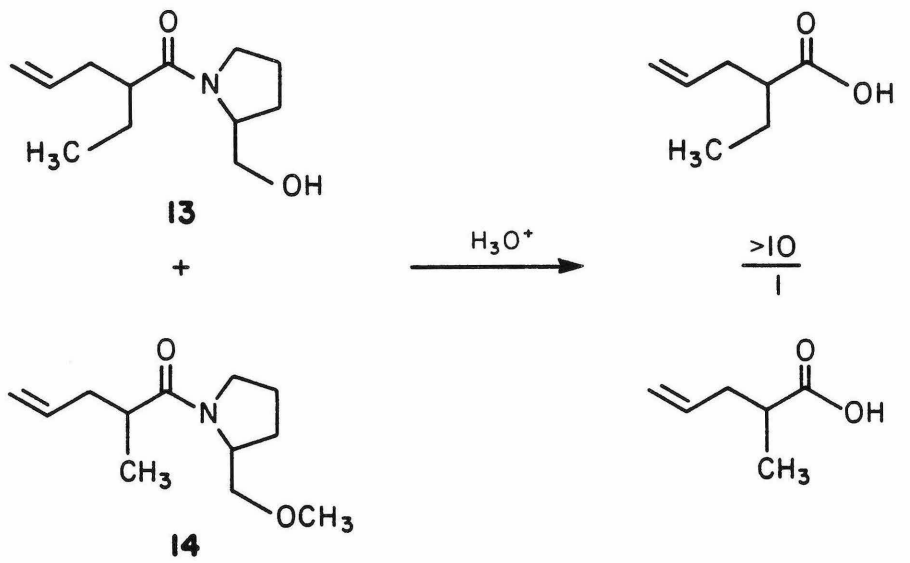


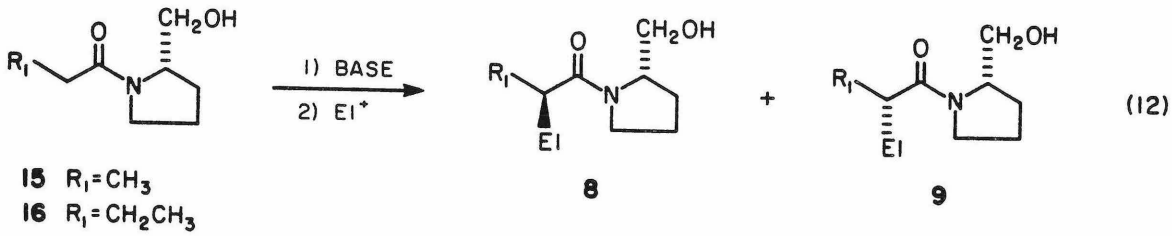
Figure 6. Hydrolysis experiments. A. Starting amide 12a. B. After refluxing in 1.0 N HCl (2 h). C. Partial thermal equilibration of ester 11a to amide 12a. D. After refluxing amide 12b in 1.0 N HCl (2 h).



(11)

C. Optimization of Dianion Alkylation Conditions. The ionic character of the metal enolate bond, the solubility, and the state of aggregation in solution might all effect the eventual stereochemical outcome of the alkylation reaction. The transition state bond distance, which in turn reflects the magnitude of the non-bonded interactions that will presumably determine the degree of enolate side differentiation, depends on the steric and electronic nature of both enolate and electrophile. It can be expected from these considerations that the delicate series of equilibria which must

be accommodated to achieve highly diastereoselective alkylation will be critically dependent on the reaction conditions (eq 12). A fluctional nature and many degrees of freedom are available to these acyclic systems. In direct contrast to other processes (i.e. aldol, cycloadditions, carbonyl additions, etc.), the lack of a well defined transition state drastically lowers the capabilities for a priori predictions. This, combined with the relatively large number of experimental variables, vide infra, and the difficulty in analysis poses a very challenging problem in optimizing the precise combination of reaction conditions to yield the desired diastereoselection. The complexity of the problem was borne out in the laboratory; and initially, reaction conditions had to be optimized for each pair of substrates. After a good deal of experimentation, however, some empirical correlations and generalizations were made.



(12)

As summarized in Table 3, diastereoselection as demonstrated by the alkylation of 15 with ethyl iodide (eq 12) is relatively independent, within the accuracy of this analysis, of the lithium base or enolization temperature employed. This is particularly surprising in the case of sec-butyllithium deprotonation (Table 3, Entry H) which should give a mixture of enolate geometries in analogy to our model studies. In contrast to our initial projections, prolinol derived amides seem to represent the first class of chiral propionate equivalents which alkylate with the same sense of asymmetric induction regardless of enolate geometry.[9,10] Enolization in the absence of lithium cations (Table 3, Entry K) gives an intermediate which alkylates stereorandomly, suggesting in light of the apparent enolate geometry independence, the crucial role of metal counterion size and Lewis acidity in orienting the chiral auxiliary via chelation (vide infra).

It has been well documented that the solubility, ionic character, and degree of solution aggregation of metal enolates is highly dependent on the solvating medium.[28] These effects can be expected to greatly influence the observed asymmetric induction. The results summarized in Table 4 show empirically this to be the case. Reaction in THF or solvent mixtures with

Table 3. Effect of Enolization Conditions on the Diastereoselectivity of Ethyl Iodide Alkylation (eq 12).

Entry	Metallation Conditions (hrs)[a]	Alkylation Conditions (hrs)	Ratio (8:9)[b]
A	LDA/-78°C (0.3)	-78°C (7)	92:8
B	LDA/-78° → 0°C (0.7)	-78° → 25°C	88:12
C	LDA/25°C (0.5)	-78°C (4)	94:6[c]
D	LDA/25°C (0.7)	25°C	92:8
E	LDA/25°C (0.7)	5% HMPA/25°C	90:10
F	LDA/25° → 65°C (2)	25°C	89:11
G	LDA/10% HMPA/25°C (0.3)	10% HMPA/25°C	93:7
H	s-BuLi/-78°C (0.1)	-78° → 25°C	92:8
I	s-BuLi/-78° → 25°C (1)	-78° → 25°C	86:14
J	KDA/0°C (0.2)[d]	25°C	92:8[c]
K	K HMDS/65°C (2)[e]	25°C	49:51[c]

[a]All reactions run in THF. [b] Ratio (8:9; Eℓ = CH_2CH_3) determined by integration of peak area on gas chromatography (1/8" SS 10' Carbowax 20M). Averaged value ±3%. [c]Reaction <50% complete. [d]Prepared by reaction of t-BuOK, n-BuLi and $(i\text{-Pr})_2NH$. [e]Prepared by reaction of KH with $(TMS)_2NH$.

HMPA appears to be generally applicable. Alkylations performed in ether or dimethoxyethane (DME) show much lower selectivity than the corresponding reactions performed in THF or THF-HMPA mixtures (Table 4, Entries A vs B;

Table 4. Effect of Solvent on Alkylation Diastereoselection (eq 12).

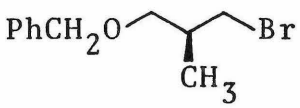
Entry	Amide	Electrophile	Metallation[a]	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
A	15	CH_3CH_2I	THF	-78° → 25°C	88:12	7.3:1
B	15	CH_3CH_2I	ether	-78° → 25°C	77:23	3.4:1
C	15	CH_3CH_2I	THF	25°C	92:8	11.5:1
D	15	CH_3CH_2I	THF	5% HMPA/25°C	90:10	9:1
E	15	CH_3CH_2I	THF	20% HMPA/25°C	89:11	8:1
F	15	CH_3CH_2I	DME	25°C	81:19	4.3:1
G	15	$PhCH_2Br$	THF	-78° → 25°C	88:12	7.3:1
H	15	$PhCH_2Br$	ether	-78° → 25°C	51:49	1:1
I	16	CH_3I	THF	-78° → 25°C	90:10	9:1
J	16	CH_3I	ether	5% HMPA/25°C	89:11	8:1

[a]Metallation with LDA (25°C, 0.5 h) in the indicated solvent. [b]Ratio (8:9) determined by integration of the peak area on gas chromatography (1/8" SS 10' Carbowax 20M). Averaged value ±3%.

C vs F; G vs H).

A study of a variety of electrophiles shows a marked effect on the nature of the leaving group. For a given alkyl moiety, iodides are optimal. Tosylates or bromides are much less satisfactory (Table 5, Entries C, G, I, K, M). Methyl tosylate reacts with a selectivity of $<5:1$ as compared to methyl iodide where the selectivity is $>15:1$ (Entry A). Dimethyl sulfate, which was the optimal reagent found for chiral oxazoline alkylation, again is less satisfactory ($<7:1$, Entry B). Similarly, the observed selectivities of 3-butenyl bromide and <u>iso</u>-butyl bromide are less than half that of the iodides under the identical reaction conditions (Entries, G. H, K, L). The origin of the very subtle transition state changes which must account for such altered selectivity is open only to speculation, however these observations quite dramatically point out the difficulty in understanding acyclic stereoselection. In the case of benzylic halides, bromides appear to be optimal. Perhaps this indicates that high diastereoselection depends more on a certain reactivity level rather than the necessity for a particular leaving group. This interpretation is, however, based only on the class of electrophiles which shows an atypically poor performance in the chiral amide alkylation, both in terms of selectivity and

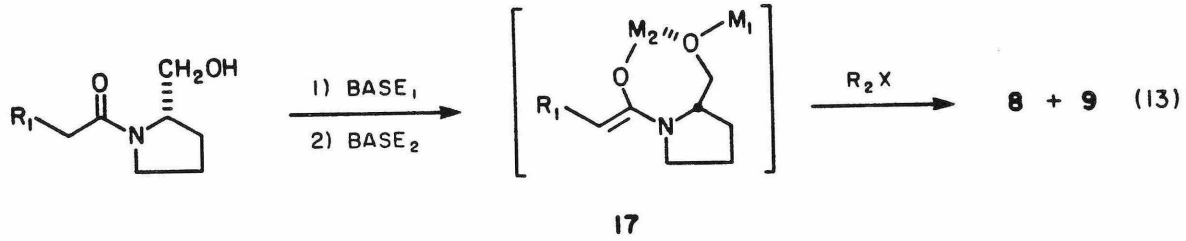
Table 5. Effect of Electrophile Leaving Group on Alkylation Diastereoselection (eq 12).[a]

Entry	Amide	Electrophile	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
A	16	CH_3I	4% HMPA/-100°C	93.9:6.1	15.4:1
B	16	$(CH_3)_2SO_4$	4% HMPA/-78°C	87.4:12.6	6.9:1
C	16	CH_3OTs	4% HMPA/-78°C	82.1:17.9	4.6:1
D	15	$PhCH_2Cl$	-78°C	81.4:18.6	4.4:1
E	15	$PhCH_2Br$	-100°C	91.2:8.8	10.4:1
F	15	$PhCH_2I$	-78°C	88.0:12.0	7.3:1
G	15	$CH_2{=}CHCH_2CH_2Br$	25°C	74:26[c]	2.8:1
H	15	$CH_2{=}CHCH_2CH_2I$	25°C	86.3:13.7	6.3:1
I	15	$CH_2{=}CHCH_2CH_2OTs$	5% HMPA/-78°C	65.8:34.2	1.9:1
J	15	$CH_2{=}CHCH_2CH_2I$	5% HMPA/-78°C	92.4:7.6	12.2:1
K	15	i-C_4H_9Br	25°C	57.8:42.2	1.4:1
L	15	i-C_4H_9I	25°C	94.4:5.6	16.9:1
M	15		25°C	73.8:26.2	2.8:1

[a]All reactions performed in THF with deprotonation by LDA (25°C, 0.5 h). The reported conditions are for comparison purposes and are not necessarily optimal for the given substrates. [b]Diastereomer ratio (8:9) determined by integration of the peak areas on gas chromatography (fused glass capillary column). [c]Diastereomer ratio estimated from ^{13}C NMR.

reproducibility, possibly reflecting spurious reaction pathways.

A systematic survey of metal counterion effects in the alkylation of dianion 17 produces some interesting results (eq 13). The magnesium enolates (Table 6, Entries A-G) show both low reactivity and low selectivity (< 3:1). Solvent effects are important with ether (Table 6, Entry F), again showing the lowest selectivity. It is interesting to note that the magnesium enolate is reported as optimal in the alkylation of ephedrine derived amides (Appendix I).[5c,d] The topology of the two systems might well be quite different, particularly due to the presence of the pyrrolidine ring in the prolinol derived amides which should significantly serve to rigidify this system.



In contrast to the dilithio anion which shows an optimal selectivity with ethyl iodide of >11:1, the dipotassium enolate, 17 (M_1 = M_2 = K), reacts under identical conditions in a completely stereorandom

Table 6. Effect of Metal Counterion (17) on Alkylation Diastereoselection (eq 13).

Entry	Amide	M_1	M_2	Metallation Conditions[a]		Electrophile	Alkylation	Ratio (8:9)[b]	Selectivity
A	15	Mg		THF	1) LDA 2) $MgBr_2$[c]	CH_3CH_2I	5% HMPA 25°C	71:29	2.4:1
B	15	Mg		THF	1) LDA 2) $MgBr_2$[c] (2 eq)	CH_3CH_2I	5% HMPA 25°C	73:27[d]	2.7:1
C	15	Mg		THF	1) LDA 2) $MgBr_2$[c]/65°C (2h)	CH_3CH_2I	25°C	70:30	2.3:1
D	15	Mg		THF	1) LDA 2) $MgBr_2$[e]	CH_3CH_2I	25°C	71:29	2.4:1
E	15	Mg		DME	1) LDA 2) $MgBr_2$[e]	CH_3CH_2I	25°C	75:25	3.0:1
F	15	Mg		ether	1) LDA 2) $MgBr_2$[e]	CH_3CH_2I	25°C	56:44[d]	1.3:1
G	16	Mg		ether	1) LDA 2) $MgBr_2$[e]	CH_3I	3% HMPA 25°C	70:30	2.3:1
H	15	Li	Li	THF	1) LDA	CH_3CH_2I	25°C	92.0:8.0	11.5:1
I	15	Li	Na	THF	1) NaH 2) LDA	CH_3CH_2I	25°C	82:18	4.6:1

Table 6. Continued

Entry	Amide	M_1	M_2	Metallation Conditions[a]		Electro-phile	Alkylation	Ratio (8:9)[b]	Selectivity
J	15	Li	K	THF	1) KH 2) LDA	CH_3CH_2I	25°C	85.3:14.7	5.8:1
K	15	K	K	THF	1) KHMDS[f]/65°C (2h)	CH_3CH_2I	25°C	49:51[d]	1:1
L	15	Li	Li	THF	1) LDA	CH_3CH_2I	4% HMPA -100°C	90.7:9.3	9.8:1
M	15	Li	K	THF	1) KH 2) LDA	CH_3CH_2I	5% HMPA -78°C	93.9:6.1	15:1

[a]Metallation performed at 25°C (0.5 h) in the indicated solvent. [b]Ratio (8:9) determined by integration of the peak areas on gas chromatography. Entries A-G, I, K (1/8" SS 10' Carbowax 20M) averaged value ±3%. Entries H, J, M, L (capillary column, see Experimental Section, fused silica glass. [c]Added as the THF complex. [d]Reaction proceeded to < 50% completion. [e]Added as an ether solution. [f]Prepared by the reaction of KH with $(TMS)_2NH$ in THF.

fashion. The drastic differences in comparable reactions (Table 7, Entries D, H, K), probably reflect significant differences in the equilibrium bond lengths, angles and strengths in the proposed transient chelate 17 (*vide infra*).

It was anticipated that the nature of the chelating arm of the chiral auxiliary would be of critical importance in effecting high diastereoselection. In an effort to enhance the chelating ability of this moiety by increasing its basicity relative to the lithium salt but hopefully without altering many of the other features which make the dilithio enolate 17 successful, we examined the reaction of mixed lithium-potassium dianion 17. Formed by pretreatment of hydroxyamide 15 (R_1 = CH_3) with potassium hydride to yield the more basic potassium alkoxide followed by addition of one equivalent of LDA, the alkylation of this species is again quite complicated. Under certain conditions, however, higher selectivity is observed. Low temperature alkylation of the mixed enolate system with ethyl iodide in THF-HMPA mixtures show about 15:1 selectivity as compared to about 10:1 for the dilithio species under similar conditions (Table 6, Entries L, M).

The aforementioned studies (Tables 3-6) serve in our minds to define from the overwhelming myriad of

potential variations, four promising sets of reaction conditions for the dianionic substrates 17. Alkylation of the dilithium or mixed lithium-potassium LDA generated enolate in either THF or 5% HMPA in THF (2.1 equiv HMPA), must now be selected with regard to the temperature and the structure of alkyl iodide or allylic bromide employed. Table 7 summarizes a number of experiments grouped in terms of the electrophilic component and itemized according to the starting amide (*vide infra*) and the four sets of reaction conditions described above. It is immediately obvious that no one set of conditions is universally applicable.

The normal iodoalkanes show their highest diastereoselectivity (>15:1) in reaction with the mixed salt (Method B) in the presence of HMPA (Table 7, Entries 15, 18). In the absence of HMPA, this system is the least satisfactory. Perhaps more interestingly, the corresponding reactions of the dilithio enolate in THF solution are only slightly less selective (Entries 7, 16, 17). These reactions as well as the examples of dilithio enolate (Method A) in the presence of HMPA show, in contrast to our initial expectations, a minimal temperature effect. The diastereomer ratio obtained at 25°C is, within experimental error, the same as is obtained by reaction at -78°C. In a practical

Table 7. Trends in Diastereoselection as a Function of Electrophile Structure (eq 13).

Entry	Amide	Metallation[a]	Electrophile	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
1	16	A	CH_3I	4% HMPA -78°C	93.9:6.1	15.4:1
2	16	A	CH_3I	4% HMPA -100°C	94.2:5.8	16:1
3	18	A	CH_3I	3% HMPA -100°C	90.4:9.6	9.4:1
4	19	A	CH_3I	25°C	82.7:17.3	4.8:1
5	19	A	CH_3I	-78°C	83.1:16.9	4.9:1
6	19	B	CH_3I	25°C	86.0:14.0	6.1:1
7	15	A	CH_3CH_2I	25°C	92.0:8.0	11.5:1
8	15	A	CH_3CH_2I	-40°C (4 h)	92:8[c]	11.5:1
9	15	A	CH_3CH_2I	-78°C (4 h)	94:6[c,d]	15.7:1
10	15	A	CH_3CH_2I	5% HMPA 25°C	90:10[c]	9:1
11	15	A	CH_3CH_2I	20% HMPA 25°C	89:11[c]	8:1

Table 7. Continued

Entry	Amide	Metallation[a]	Electrophile	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
12	15	A	CH_3CH_2I	5% HMPA -78°C	89:11[c]	8:1
13	15	A	CH_3CH_2I	4% HMPA -100°C	90.7:9.3	9.8:1
14	15	B	CH_3CH_2I	25°C	85.3:14.7	5.8:1
15	15	B	CH_3CH_2I	5% HMPA -78°C	93.9:6.1	15:1
16	15	A	$CH_3CH_2CH_2CH_2I$	25°C	94.1:5.9	16:1
17	15	A	n-$C_8H_{17}I$	25°C	91.7:8.3	11:1
18	15	B	n-$C_8H_{17}I$	5% HMPA -78°C	94.5:5.5	17:1
19	15	A	$CH_2{=}CHCH_2CH_2I$	25°C	86.3:13.7	6.3:1
20	15	A	$CH_2{=}CHCH_2CH_2I$	5% HMPA -78°C	92.4:7.6	12.2:1
21	15	A	$CH_2{=}CHCH_2Br$	25°C	83.7:16.3[e]	5.1:1
22	15	A	$CH_2{=}CHCH_2Br$	-60°C	91:9[f,g]	10:1
23	15	A	$CH_2{=}CHCH_2Br$	-78°→25°C	87:13[f,h]	6.7:1

Table 7. Continued

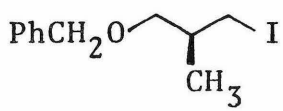
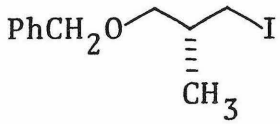
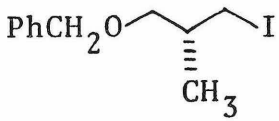
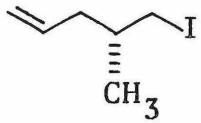
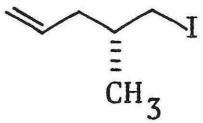
Entry	Amide	Metallation[a]	Electrophile	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
24	15	A	$CH_2{=}CHCH_2Br$	6% HMPA -78°C	93.7:6.3	14.9:1
25	15	A	$CH_2{=}CHCH_2Br$	DMI[i] -78°C	87.6:12.4	7.1:1
26	15	A	$CH_2{=}CHCH_2Br$	5% HMPA -100°C	96.2:3.8	25:1
27	15	B	$CH_2{=}CHCH_2Br$	25°C	77.1:22.9	3.4:1
28	15	B	$CH_2{=}CHCH_2Br$	5% HMPA -78°C	91.2:8.8	10.4:1
29	15	B	$CH_2{=}CHCH_2Br$	6% HMPA -100°C	94.8:5.2	18:1
30	15	A	i-C_4H_9I	25°C	94.4:5.6	16.9:1
31	15	A	i-C_4H_9I	5% HMPA -100°C	97.6:2.4	41:1
32	15	B	i-C_4H_9I	0°C	92:8[f]	11.5:1
33	15	B	i-C_4H_9I	-78°→-20°C	82.7:17.3	4.8:1
34	15	A		5% HMPA -100°C	98.2:1.8	55:1

Table 7. Continued

Entry	Amide	Metallation[a]	Electrophile	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
35	15	A		5% HMPA -100°C	94.8:5.2	18:1
36	15	B		5% HMPA -78°C	98.1:1.9	52:1
37	15	A		5% HMPA -78°C	95.7:4.3	22:1
38	15	B		5% HMPA -78°C	96.8:3.2	30:1

[a]Method A: Metallation with LDA (25°C, 0.5 h) in THF. Method B: Treatment of hydroxy-amide with KH followed by addition of LDA (25°C, 0.3 h) in THF. [b]Diastereomer ratio (8:9) determined by integration of the peak areas on gas chromatography (capilalry VPC, fused silica glass) unless otherwise noted. [c]VPC analysis (1/8" SS Carbowax column, averaged value ±3%). [d]Reaction proceeded to <50% completion [e]Ratio (8:9) 84:16 determined by ^{13}C analysis. [f]Determined by ^{13}C analysis. [g]Reaction run 36 h at -60°C. [h]The internal temperature at which alkylation in the absence of HMPA occurs at an appreciable rate for these substrates is not clear. [i]Saturated, <4% of 1,3-dimethyl-2-imidazolidinone in THF (-78°C).

sense none of the low temperature reactions done in the absence of HMPA proved particularly convenient due to often unpredictable reaction times and occasional precipitation of the dianion intermediate 17. We would have projected from Figure 2, that the selectivity should be about halved over that temperature range. Recall that Figure 2 was based on a very simple model and indeed these diastereomeric amide transition states have proved to be quite complicated and unpredictable. This apparent self-compensation as a function of temperature, which supplants the normal reactivity-selectivity principles, represents yet another example. In a practical sense, if slightly lower selectivity (11:1) can be tolerated, alkylation at ambient temperatures and in the absence of the carcinogenic HMPA provides an appealing alternative procedure for the introduction of normal alkyl chains.

Alkylation with allyl bromide is subject to different constraints (Table 7, Entries 21-29). It appears that, regardless of the conditions employed, high diastereoselection is observed only at low temperature (Entries 21, 22). The normal selectivity enhancement with temperature reduction is apparent even over relatively small temperature changes (Entries 24, 26, 28, 29). Optimal conditions (25:1) use the dilithio enolate 17

in THF-HMPA solution at -100°C (Entry 26). It is important to note that no special problems or loss in this high selectivity were observed on scaling-up from 5 to >40 mmol, indicating that even larger quantities of material should be readily available by this method. The corresponding mixed salt 17 is only slightly less selective (18:1, Entry 29). This trend is preserved in comparable reactions in the absence of HMPA (Entries 21, 27). It is interesting to note that substitution of 1,3-dimethyl-2-imidazolidinone, an advertised HMPA replacement, substantially lowers the selectivity (7.1:1, Entries 24, 25).

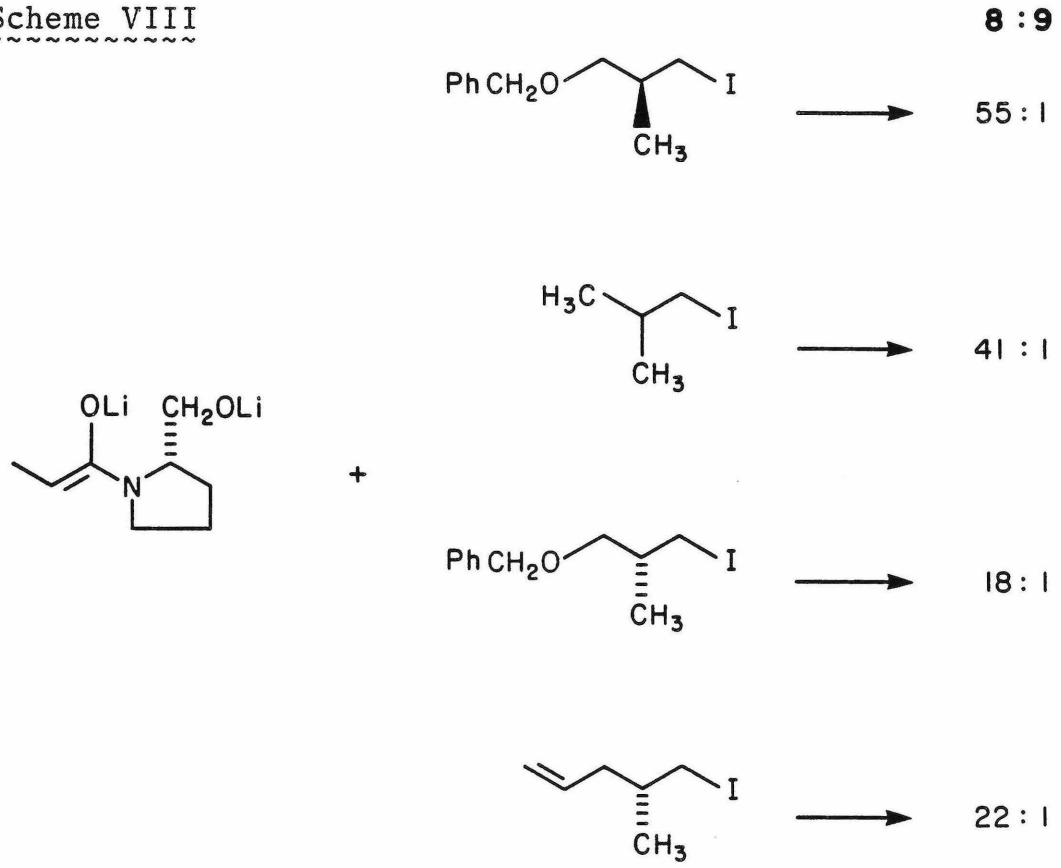
Iodides with branching β to the reacting center alkylate (Table 7, Entries 30-38) with exceptionally high diastereoselectivity (>30:1). As with the saturated normal alkanes, the apparent optimal conditions employ the lithium-potassium dianion (Method B) and low temperature alkylation in 5% HMPA-THF (Entries 36, 38). In this case, however, it is the low temperature reaction of the dilithio enolate (Method A) in THF-HMPA solution (Entries 31, 34, 37) that provides the almost equally useful alternative procedure (selectivity >20:1) and not its reaction at ambient temperatures (<12:1, Entries 30, 32) as noted in the earlier case.

To explain the generally higher diastereoselection

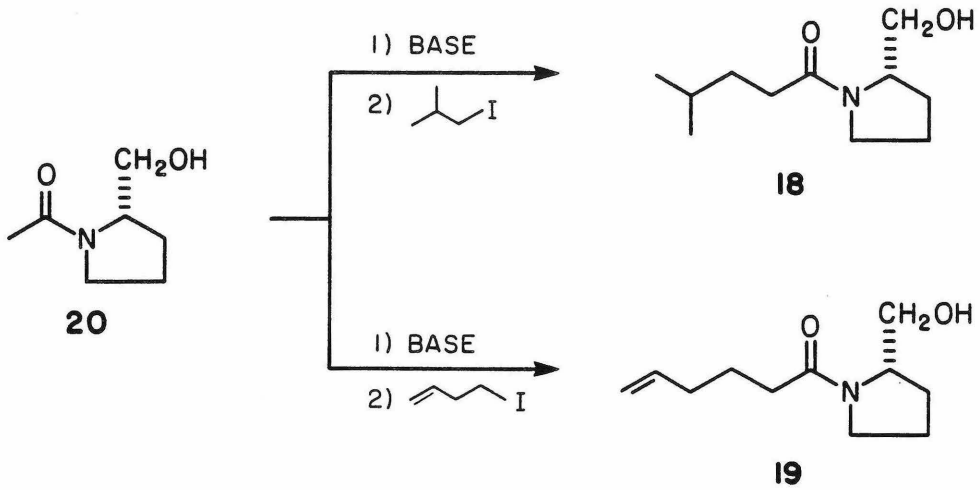
observed in the β-branched electrophiles (>30:1) relative to the straight chain iodides (≤17:1) one might suspect a quite remote interaction between the chiral auxiliary on the enolate and the β-center of the electrophile. Additional evidence for this can be gained from Table 7. The appropriate results are summarized in Scheme VIII. The diastereoselection at the newly formed center varies smoothly in accord with the absolute configuration of the resident β-center. Selectivity of about 41:1 in the parent achiral iodide is seemingly reinforced by an inherent preference in the reactivity of the S-iodide to increase the overall selection (55:1), but opposed by the inherent selectivity of the R-iodide to yield a lower net induction (18:1). This provides the first evidence for small but measurable double diastereodifferentiation from a remote center in an asymmetric alkylation.[30,31]

Methylations, which would yield the opposite absolute configuration at the newly formed center relative to propionamide alkylation, have been only briefly examined. In simple systems such as amide **16**, these proceed with high efficiency (>16:1, Table 7, Entry 2). Although not fully optimized, more complicated substrates seem to show somewhat lower selectivity (<10:1, Entry 3). This approach was abandoned primarily because of the

Scheme VIII



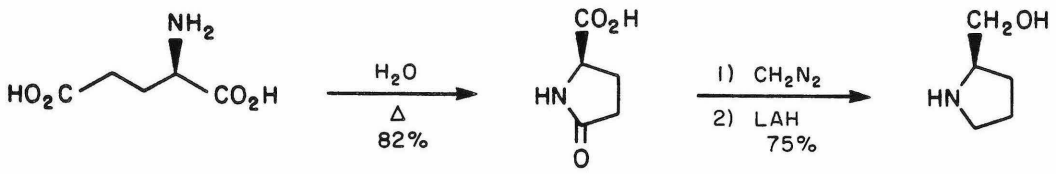
need to synthesize and isolate the requisite starting amide. Typically these would be available by alkylation of the prolinol acetamide derivative 20 (eq 14). Amide 20 available, as before, by acylation with acetic anhydride, is somewhat more difficult to purify and store due to apparent N → O acyl transfer. In addition, although alkylation under optimal conditions (1. KH; 2. LDA; 3. RI/HMPA/25°C) proceeds in good yield, dialkylation,



(14)

which is not observed in the more highly substituted amides, comprises about 10% of the reaction product. Our initial goal of an efficient one-pot sequential alkylation-methylation sequence was not available with these amides.

The application of prolinol derived propionamide as a chiral reagent for the construction of either absolute configuration of a methyl bearing center α to a carbonyl is, however, at hand. Although the naturally occurring form of proline is of the S-configuration, R-prolinol is readily available by cyclization and reduction of D-glutamic acid in a procedure reported

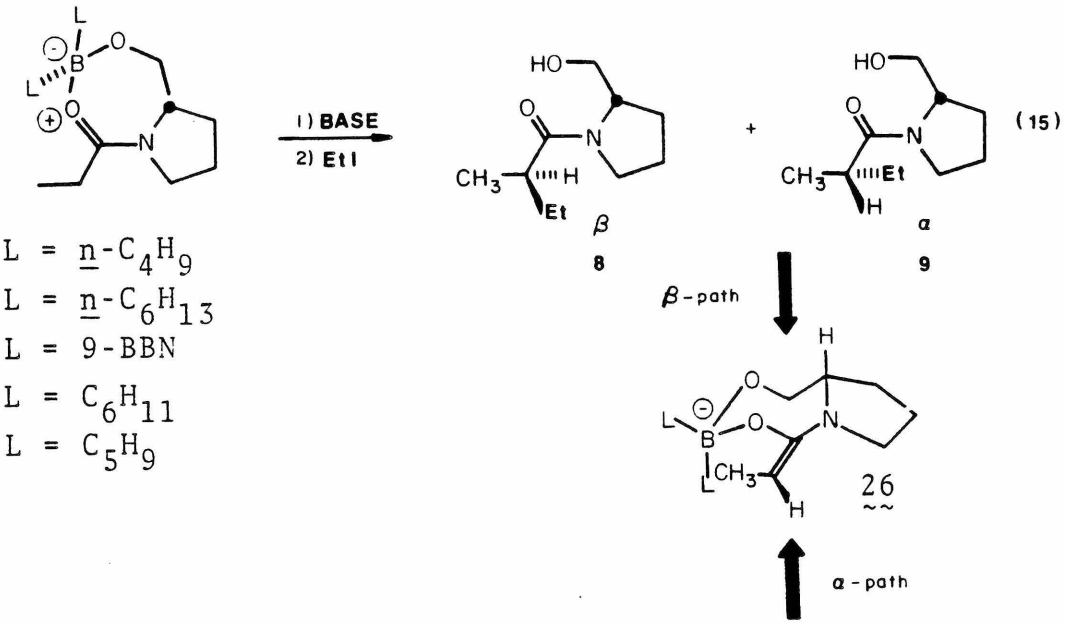


during the course of this work by Enders.[32]

In spite of the large number of potentially important reaction variables, the rather complicated studies on hydroxyamide alkylations can be quite simply summarized. The mixed salt method, which utilizes pretreatment of hydroxyamide with KH followed by one equivalent of LDA and subsequent low temperature reaction of an alkyl iodide in 5% HMPA-THF, is the procedure of choice. Allylic bromides best employ the dilithio enolate generated from two equivalents of LDA under otherwise identical conditions. The other procedures discussed above and demonstrated in Table 7 may show, depending on the electrophile, almost equally efficient diastereoselection and in certain cases have practical implications which would favor their application. If the R-configuration is desired at the newly formed center, the S-prolinol derived hydroxypropionamide is employed.

If the S-configuration needs to be constructed, the R-hydroxyamide is used.

D. Alkylation of Boron-Ate Complexes. In line with our interest in using metal center steric effects to control stereochemistry, we have examined the reaction of alkoxyborane amide derivatives 21-25. Enolization and internal complexation gives an intermediate such as 26 in which the chiral auxiliary serves to fix the orientation of the covalently bonded ligands on boron to reinforce the diastereoisomeric bias. In addition to introducing a new controllable steric component to the

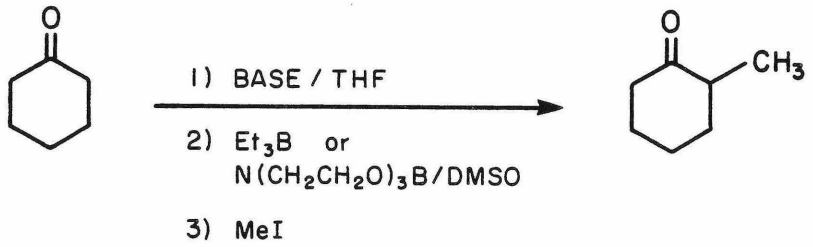


21, L = n-C_4H_9
22, L = n-C_6H_{13}
23, L = 9-BBN
24, L = C_6H_{11}
25, L = C_5H_9

reaction, the ate-complexes offer several other possible advantages. The complex is likely to exist as a monomer in solution avoiding the complications associated with

aggregation. The relatively strong boron-oxygen bond and lower reactivity of these intermediates, as compared to the alkali metal enolates suggest, they might be subject to much more stringent stereoelectronic constraints. Reaction through a much tighter, well-defined transition state could lead to enhanced diastereo face discrimination.

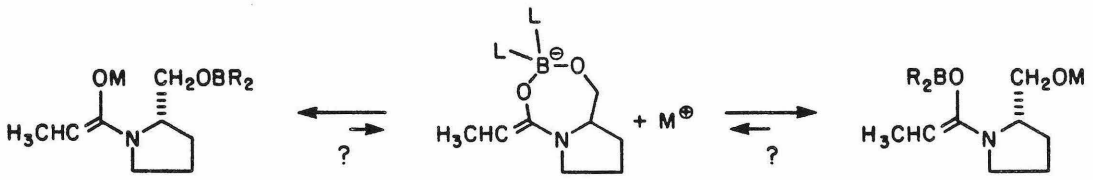
The boronate complexes of ketone enolates have been alkylated by Rathke[33] and Negishi.[34,35] Addition of triethylborane or triethanolamineborate to the alkali metal enolate gives a species, which in contrast to the precursor, undergoes clean monoalkylation (eq 16). The workers also, however, uncovered several potential



(16)

complications in applying this approach to the chiral hydroxy amides. The readily reversible bimolecular complexation is quite dependent on the metal counterion and sensitive to steric effects at boron.[34,36] In the initial complexation reaction, the electrophilic boron

can react either directly on oxygen or first on carbon followed by a possible 1,3 C → O migration.[37] This latter pathway carries the potential for scrambling enolate geometry and has some precedent from work in this laboratory.[38] Rathke has observed that starting with a borate which is not constrained by a ring (e.g. trimethyl, tri-tert-butylborate), complexation followed by apparent loss of alkoxide yields the unreactive boron enolate. The present case, although intramolecular, requires the kinetically less favorable seven-membered ring formation and may be subject to the equilibria described by equation 17. In fact, the limited literature data which have been used as evidence for direct alkylation of the boronate complexes may as well be consistent with alkylation through a small equilibrium amount of the more reactive alkali metal enolate. The air sensitive amides 21-25 are conveniently



27

(17)

prepared from the appropriate dialkylborane and hydroxyamide, from the dialkylchloroborane and sodium alkoxide, or from *in situ* formation of the ate-complex by addition of one equivalent of the chloroborane to a solution of preformed dianion. The ^{1}H NMR spectrum of borate **25** shows a significant downfield shift relative to the hydroxyamide for the protons α and β to the carbonyl [$\Delta\delta$ (C(O)C$\underline{H}_2$) = 0.42 ppm, $\Delta\delta$ (C(O)CH$_2$C$\underline{H}_3$) = 0.15 ppm] as would be expected from decreasing the electron density at the carbonyl carbon in a strongly intramolecularly complexed amide. Further these species undergo smooth deprotonation with LDA or potassium hexamethyldisylamide (HMDS) at ambient temperatures, while the corresponding hydroxy amide shows much lower acidity undergoing only partial (~30%) reaction with the latter reagent under forcing conditions. Dimsyl potassium is ineffective, however, even with the boron derivative.

The consequences of ethyl iodide alkylation under a variety of reaction conditions are summarized in Table 8. In certain cases high selectivity can be realized. Comparable results are obtained using either the *in situ* ate-complex preparation or *via* deprotonation of the borate (Entries 20-23).[39] Alkylation of the lithium boronate **27** in the absence of HMPA shows only low

Table 8. Akylation of Amide Enol Boronates With Ethyl Iodide (eq 15).

Entry	Amide	Metallation Conditions[a]	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
1	15	1) LDA 2) $(n\text{-}C_4H_9)_2BOTf$[c]/-78→25°C	25°C	67:33	2:1
2	15	1) LDA 2) $(n\text{-}C_6H_{13})_2BCl$/25°C	25°C	69:31	22:1
3	22	LDA	10% HMPA 25°C	77:23	3.4:1
4	23	LDA	10% HMPA 25°C	89:11	8.1:1
5	23	LDA (HF)[d]	10% HMPA 25°C	92:8	11.5:1
6	24	LDA (HF)	10% HMPA 25°C	86:14	6.1:1
7	24	LDA (HF)	20% HMPA 25°C	88:12	7.3:1
8	24	LDA (HF)	30% HMPA 25°C	90:10	9:1
9	24	LDA (HF)	10% HMPA -20°C	90:10	9:1
10	24	LDA (HF)/10% HMPA	10% HMPA 25°C	91:9	10.1:1

Table 8. Continued

Entry	Amide	Metallation Conditions[a]	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
11	24	LDA (HF)/20% HMPA[f]	20% HMPA -30°C	94:6	16:1
12	24	LDA (HF)/10% HMPA[f]	10% HMPA -30°C	90:10[g]	9:1
13	24	LDA/10% HMPA	10% HMPA -40° → 10°C	97:3	32:1
14	24	LDA/10% HMPA/-78°C[e]	10% HMPA -40° → 10°C	70:30	2.3:1
15	24	1) LDA (HF)/10% HMPA/-78°C 2) 25°C (1 h)	10% HMPA -30°C	91:9	10.1:1
16	24	1) LDA (HF)/10% HMPA 2) 65°C (1 h)	10% HMPA -30°C	88:12	7.3:1
17	24	LDA (HF)/10% HMPA[f]	10% HMPA -78°C	86:14	6.1:1
18	24	LDA (HF)/10% HMPA/-78°C[f]	10% HMPA -78° → -30°C	81:19	4.3:1
19	24	KHMDS[h]/10% HMPA[f]	10% HMPA 25°C	93:7	13.3:1
20	15	1) LDA 2) $(C_5H_9)_2BCl$/-78°C	-78° → 25°C	64:36	1.8:1

Table 8. Continued

Entry	Amide	Metallation Conditions[a]	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
21	15	1) LDA 2) $(C_5H_9)_2BCl$/25°C	25°C	63:37	1.7:1
22	15	1) LDA 2) $(C_5H_9)_2BCl$/65°C (2 h)	25°C	70:30	2.3:1
23	25	LDA	25°C	68:32	2.1:1
24	25	LDA	10% HMPA 25°C	97:3[i]	32:1
25	25	LDA	10% HMPA 0°C	94:6	16:1
26	25	LDA/-78°C	10% HMPA 0°C	94:6	16:1
27	25	LDA/20% HMPA	20% HMPA 0°C	97:3	32:1
28	25	LDA (HF)/10% HMPA[f]	10% HMPA -30°C	93:7	13.3:1
29	15	1) KH 2) $(C_5H_9)_2BCl$ 3) LDA	10% HMPA 25°C	82:18	4.6:1
30	25	KHMDS/65°C (2 h)	25°C	83:17	4.9:1

Table 8. Continued

Entry	Amide	Metallation Conditions[a]	Alkylation Conditions	Ratio (8:9)[b]	Selectivity
31	25	KHMDS	5% TMEDA[j] 25°C	83:17	4.9:1
32	25	KHMDS	5% HMPA 25°C	94:6	16:1
33	25	KHMDS	5% HMPA 0°C	95:5	19:1
34	25	KHMDS	20% HMPA 0°C	97:3	32:1
35	25	KHMDS/20% HMPA	20% HMPA 0°C	95:5	19:1

[a]All reactions run in THF with metallation by the indicated base (25°C, 0.3 h). [b]Diastereomer ratio (8:9) determined by integration of the peak areas on VPC analysis (1/8" x 10' SS Carbowax, averaged ±3%). [c]Dibutylboron triflate. [d]Hexane-free LDA. [e]Reaction run by addition of alkoxyborane to a solution of LDA in HMPA-THF. [f]Reaction run by addition of base to solution alkoxyborane in HMPA-THF. [g]Uses ethylbromide in place of ethyl iodide. [h]Prepared by the reaction of hexamethyldisilylazide with KH in THF. [i]Average of several experiments. [j]Tetramethylethylenediamine.

selectivity (< 2.4:1), regardless of the alkyl ligand on boron, to form predominantly the R absolute configuration at the newly constructed stereocenter, as was observed with the corresponding hydroxyamides (Entries 1, 2, 20-23). The potassium boronate 27 under comparable conditions is only somewhat more selective (Entry 30). Addition of a very good cation solvator, such as HMPA, prior to alkylation would be expected, just as changing from the more covalent bonding lithium to potassium, to shift any equilibrium toward boronate-complex 27 and away from any contact ion pairs (eq 17). Although depending on the relative rates of reaction this shift does not guarantee alkylation through the ate-complex, addition of HMPA is reflected by an increase in selectivity for ethylation to give the R-configuration as predicted by β attack on 26 (Table 8, Entries 2, 3; 23, 24; and 30, 32). In fact, in the case of the lithium dicyclohexylboronate complex derived from 24, selectivity increases measurably from 6:1 to 9:1 as a function of increasing HMPA concentration (Entries 6-8). A similar trend can be noted in the potassium dicyclopentylboronate complex derived from 25, in which selectivity increases from 19:1 to >30:1 by increasing the HMPA concentration from 5% to 20% (Entries 33, 34). Using hexane-free base again seems

to promote somewhat higher selectivity (Entries 4, 5). Interestingly another commonly employed solvating agent, tetramethylethylenediamine (TMEDA), is ineffective with the potassium boronate complex (Entries 30-32).

Perhaps the most interesting feature of the amidoborates is the capability to systematically vary the alkyl ligand on boron. As demonstrated in Table 8, the observed selectivity is critically tied to the structure of that substituent. The selectivity under otherwise identical conditions generally increases in accord with the steric demands of the ligand. The series of di-n-hexyl (3.4:1), dicyclohexyl (6.1:1), 9-BBN[40] (11.5:1) and dicyclopentyl (>30:1) reveals the latter be the most generally applicable substrate (Entries 3, 6, 5, 24). Under carefully optimized conditions the dicyclohexyl derivative, which avoids the tedious preparation of a dialkylchloroborane[41] in favor of the readily available crystalline dicyclohexylborane,[42] shows the same high selectivity (>30:1, Entry 13).

A number of other trends can be derived from Table 8. Addition of HMPA prior to enolization increases selectivity in the case of the lithium boronate (Entries 6, 10) but has a slightly deleterious effect when the potassium counterion is used (Entries 34, 35). Low temperature reactions, particularly in the case of the

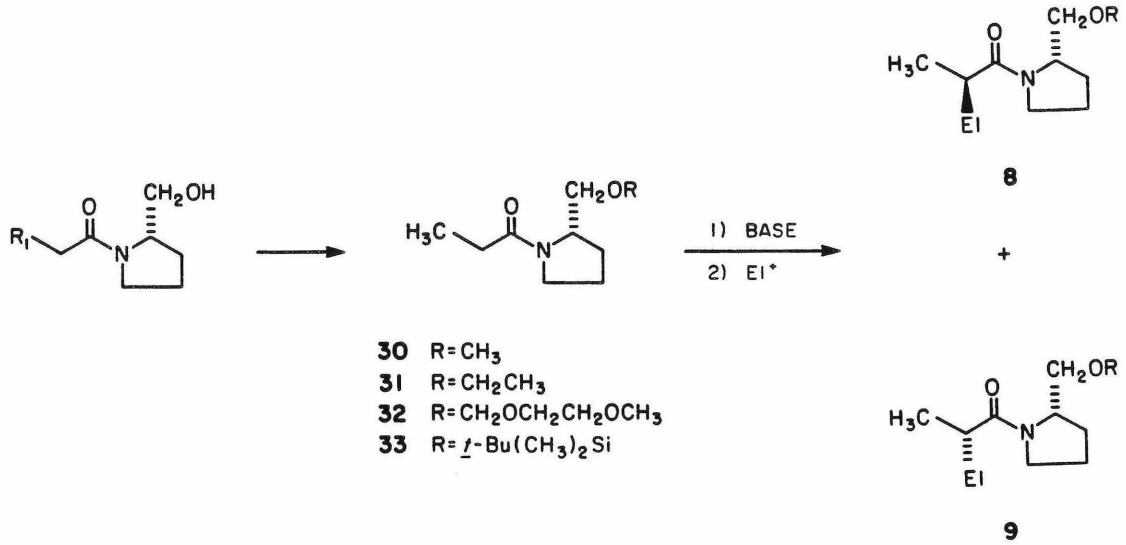
dicyclopentyl derivative, are sluggish and no clear temperature effect is discernible (Entries 6, 9, 10, 13, 17, 24, 25, 27, 28). In one example, ethyl bromide used in place of ethyl iodide showed only slightly lower (9:1) than the expected stereoselection under the given reaction conditions (Entries 11, 12).

Entries 13 and 14 (Table 8) show a final comparison of interest. These experiments which differ only in the temperature of enolization and show that low temperature (-78°C) deprotonation gives an intermediate which reacts with low diastereoselection (2.3:1) when compared to deprotonation at ambient temperatures (>30:1). Further, if that intermediate is permitted to warm prior to alkylation, high selectivity is restored (Entry 15). Entries 17 and 18 (Table 8) provide corroborating evidence. These results suggest that either complexation is slow, which seems unusual for this intramolecular reaction, conformation equilibration is slow, or a mixture of isomeric intermediate ate-complexes **27** are produced which then thermally equilibrate. This latter pathway seems most plausible, reacting as in the aforementioned discussion through kinetic attack of the intramolecular electrophilic borate on the stereochemically pure lithium enolate at carbon followed by 1,3 C → O rearrangement to give initially **27** as a

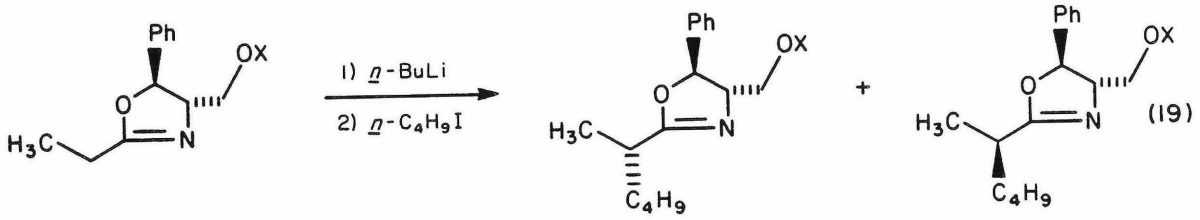
mixture of enolate geometries. Subsequent equilibration would give predominantly the cis enolate consistent with the observed results as predicted by model 26.

Although these boronate complexes, unique in their use of metal center steric effects as an approach to asymmetric alkylation, have demonstrated both interesting chemistry and synthetically useful levels of diastereoselection, application of this methodology in a preparative sense has proved to be cumbersome. The need to prepare the requisite dialkylborane, the use of large quantities of the carcinogen, HMPA, and the relative difficulty in isolating the desired product are severe drawbacks. In light of these considerations and more importantly the promising results obtained from the mechanically simplier dianions 17, the study of other alkylations in this area have not been pursued.

E. Reaction of O-Alkyl Derivatives. The hydroxymethyl side chain has been a pivotal feature in the successful diastereoselective alkylation of hydroxy amide 15. Even subtle changes in the nature of that chelating group have had, as predicted, a significant effect on the overall asymmetric induction. In a further study we have examined a series of ether derivatives 30-33 with some surprising observations (eq 18).



In contrast to the hydroxy amides, alkylation of the alkoxy propionamide gives predominantly diastereomer 9 with the S-configuration at the newly formed center. This reversal in the sense of asymmetric induction in changing from O-metal to O-alkyl was not totally unprecedented at the start of this work, but provides still another striking example of the complexity and the delicate equilibria which characterize acyclic stereoselection. Meyers reported that with an O-lithium chelating arm diastereomer 35 was slightly favored (34:35, 46:54), while with the O-methyl derivative the opposite enantiomer 34 was produced in excess (eq 19, 34:35, 72:28).[5h] During the course of this work Sonnet, studying primarily the methyl ether, has observed the identical change in the sense of asymmetric induction with prolinol as well as ephedrine derived amides.[5a,43]



	34		35
R=Li	46	:	54
R=Na	55	:	45
R=CH_3	72	:	28

Our investigations of the ether derivatives 30-33 are summarized in Table 9. It is immediately apparent that the high selectivity observed with hydroxyamides is not obtained here. A maximum selectivity of about 4.3:1 (Entries D, N) has been achieved, although one could reasonably expect somewhat higher preference if lower temperatures were employed. Selectivity increases modestly in the ethyl iodide alkylation as the temperature is decreased in THF (Entries A-C) or DME (Entries K, L), but is virtually ineffective when the reaction is run in ether (Entries H, I). In the latter two solvents alkylation is prohibitively slow at low temperatures and in the use of DME, addition of HMPA does not seem to increase the rate substantially (Entry M). Addition of HMPA prior to alkylation in cases where the reaction

Table 9. Alkylation of Alkoxy-Amide Derivatives (eq 18).

Entry	Amide	Metallation Conditions[a]	Electrophile	Alkylation Conditions (hrs)	Ratio (8:9)[b]	Selectivity
A	30	THF-LDA	CH_3CH_2I	25°C	33:67	1:2.0
B	30	THF-LDA	CH_3CH_2I	-40°C	25:75	1:3.0
C	30	THF-LDA	CH_3CH_2I	-78°C	21.9:78.1[c]	1:3.6
D	30	THF-s-BuLi	CH_3CH_2I	-78°C	19:81	1:4.3
E	30	THF-LDA	CH_3CH_2I	10% HMPA/-78°C	24:76	1:3.2
F	30	THF-LDA/HMPA	CH_3CH_2I	10% HMPA/-78°C	20:80	1:4.0
G	30	THF 1) LDA 2) $MgBr_2$	CH_3CH_2I	25°C	50:50	1:1
H	30	ether-LDA	CH_3CH_2I	25°C	22:78	1:3.6
I	30	ether-LDA	CH_3CH_2I	-40°C (4 h)	22:78[d]	1:3.6
J	30	ether-LDA	CH_3CH_2I	10% HMPA/-40°C	32:68	1:2.1
K	30	DME-LDA	CH_3CH_2I	25°C	34:66	1:1.9
L	30	DME-LDA	CH_3CH_2I	-40°C (4 h)	24:76[d]	1:3.2
M	30	DME-LDA	CH_3CH_2I	10% HMPA/-40°C	21:79[d]	1:3.8
N	31	THF-LDA	CH_3CH_2I	-78°C	19:81	1:4.3

Table 9. Continued

Entry	Amide	Metallation Conditions[a]	Electrophile	Alkylation Conditions (hrs)	Ratio (8:9)[b]	Selectivity
O	32	THF-LDA	CH_3CH_2I	-78°C	22.2:77.8[c]	1:3.5
P	33	THF-LDA	CH_3CH_2I	-78°C	23.2:76.8	1:3.3
Q	32	THF-LDA	$CH_2{=}CHCH_2Br$	-78°C	28.9:71.1	1:2.5
R	33	THF-LDA	$CH_2{=}CHCH_2Br$	-78°C	37.7:62.3	1:1.7
S	33	THF-LDA	i-C_4H_9Br	-78°C	34.5:65.5	1:1.9
T	33	THF-LDA	i-C_4H_9I	-78°C	25.6:74.4	1:2.9

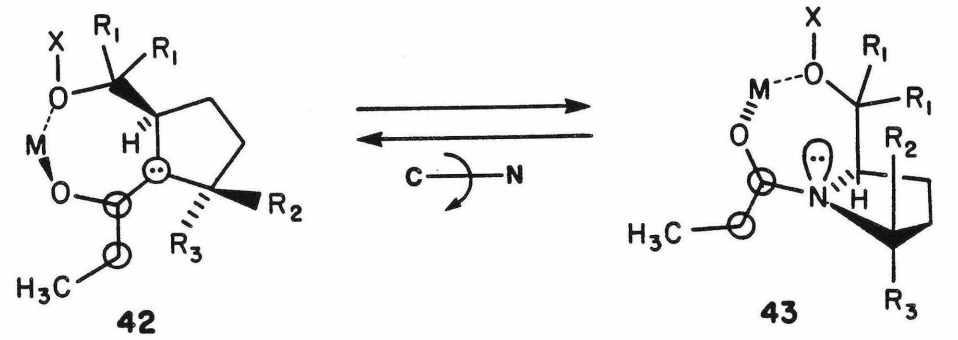
[a]Metallation by addition of amide to one equivalent of base in the indicated solvent. [b]Diastereomer ratio (8:9) determined by integration of the peak areas on VPC analysis (1/8" x 10' SS Carbowax 20M, averaged value ±2%. [c]Capillary VPC analysis. [d]Reaction proceed to <50% completion.

medium is ether or THF generally decreased selectivity by a few percent (Entries E, J). Enolization conditions are as with the hydroxyamides almost inconsequential. Deprotonation with LDA, LDA in the presence of HMPA or sec-butyllithium all result in diastereomer ratios between 3.6-4.0:1 (Entries C-F). Substitution of the magnesium counterion again gives an intermediate which alkylates in a stereorandom fashion (Entry G).

A number of ether substituents were tested. Of particular interest are the TBS and the methoxyethoxymethyl (MEM) derivatives which under the amide hydrolysis conditions are cleavaged to reveal the hydroxyl moiety. These retain the feature of facilitated amide hydrolysis by acyl transfer. The latter case also contains additional oxygen atoms in the chain which might have been expected to promote better chelation. All the derivatives show quite comparable selectivity yielding between 77% and 81% of diastereomer **9** after ethylation (Table 9, Entries C, N, O, P). Alkylation with allyl bromide or iso-butyl iodide was slightly less selective (1.7-2.9:1, Entries Q, R, S, T).

F. Other Substrates. The complexity of these bimolecular chiral amide alkylations seemingly defies a detailed transition state analysis and understanding. Our mechanistic interest, aroused primarily by the

intriguing reversal in stereochemical preference of the ether derivatives 30-33, has led us though to examine a number of structurally modified amides. In attempting to understand at least a few more of the details of this useful synthetic method and defining a simple model which suggests further experiments, we hoped to be able to design even more efficient chiral propionates for the control of acyclic stereochemistry. Consider a very simplistic representation of the extreme rotomeric forms of the chelated prolinol amide enolate 42 and 43. Note that merely by a 90° rotation about the C-N bond,



(20)

α- ATTACK FAVORED β- ATTACK FAVORED

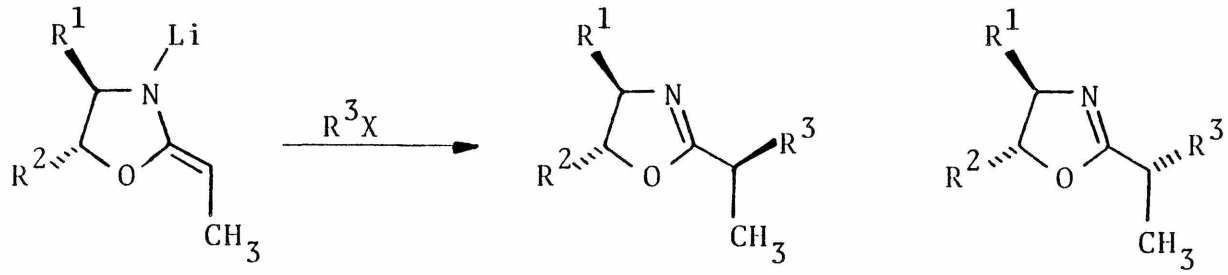
the steric differentiation imposed by the chiral auxiliary on the α and β faces of the enolate system reverses.

In the literature, the models to explain diastereoselective alkylation invoke complexation of the leaving

group of the incoming electrophile with the metal of the enolate system.[5e] Although one might well expect a stereoelectronic effect, electrophilic catalysis, or coulombic interaction to make positioning of the metal ion influential, the literature data in our estimation do not justify this as the major factor in high diastereoselection. Rather as summarized in Scheme IX, the selectivity decreases dramatically from >6:1 to < 2:1 as R^2 is made <u>less</u> sterically demanding in changing from phenyl to methyl to hydrogen (Entries A-C and D-F).[5g,k] Further as R^1, which is situated on the opposite face from R^2, is made more sterically demanding the sense of asymmetric induction reverses (Entries F, G). This smooth correlation is quite surprising in light of the distance between reacting center and the steric bias.

Consider the models, which we hoped would suggest some interesting experiments, illustrated in equation 20. We focus on the steric effects in orientation of the chiral center. We naively disregard for the present discussion other conformation effects of the seven-membered ring chelate. The fact that we've assumed both a hybridization state and absolute configuration at the nitrogen, and any concurrent bond reorganization in the transition state of the bimolecular reaction is ignored.

Scheme IX

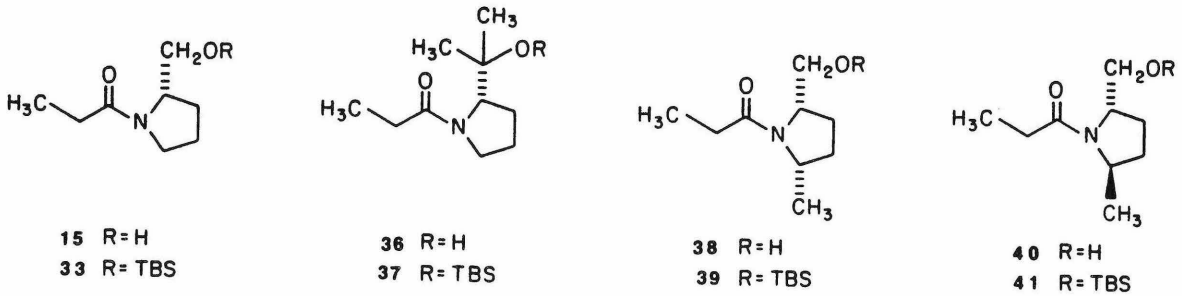


Entry	R^1	R^2	R^3X			Selectivity
A	CH_2OCH_3	Ph	$PhCH_2Br$	87	13	6.7:1
B	CH_2OCH_3	CH_3	$PhCH_2Br$	73.6	26.4	2.8:1
C	CH_2OCH_3	H	$PhCH_2Br$	61.8	38.2	1.6:1
D	CH_2OCH_3	Ph	nC_4H_9I	89	11	8.1:1
E	CH_2OCH_3	CH_3	nC_4H_9I	53.6	46.4	1.2:1
F	CH_2OCH_3	H	nC_4H_9I	51.7	48.3	1.1:1
G	$C(CH_3)_2OCH_3$	H	nC_4H_9I	12.5	87.5	1:7

Structure 42, assuming the nitrogen is in conjugation with the π system, sterically predicts attack from the α-face. This mimics the sense of diastereoselection obtained in the alkylation of the dianion derived from hydroxyamide 15, with both metal ions in a position to participate by a bridged chelation. A 90° rotation about the C-N bond, accommodating perhaps a new equilibrium chelating-bond distance, gives the other extreme rotomer, structure 43. Assuming the nitrogen lone pair is now orthogonal to the π system, the steric bias which is imposed should direct electrophilic attack from the β-face and mimics, assuming no change in enolate geometry, the sense of diastereoselection from ethers 30-33. At first isomer 43 seems unreasonable because resonance stabilization (7-10 kcal) has been lost in twisting the lone pair from what is apparently the most stable conformation on the basis of X-ray studies.[44] Studies on N-acyl enamines, however, show the orthogonal rotomer to be the most stable by >7 kcal.[45] In the present suggestion 43, note that any degree of charge on the enolate carbon will lower the resonance stabilization energy of lone pair overlap. Direct alkylation of 43 without concurrent bond reorganization, however, leads to the twist form of the amide which is about 20 kcal higher in energy than the

planar form. This might be expected to at least be partially reflected in the activation energy.

In spite of all the uncertainties these models have proved useful. They predict that the origin of the steric effects which define the observed selectivities are quite different and have led us to the more highly substituted amides 36-41 in an attempt to exploit those differences. The results of those alkylation studies



are summarized in Table 10. Amide 36, incorporating a gem-dimethyl group on the chelating side chain, is easily prepared from the appropriate proline derived amido-ester and methyl grignard. Alkylation of the lithium dianion with ethyl iodide shows slightly lower selectivity (8:1) than the parent propionamide 15 (11.5:1) under identical conditions (Table 10, Entries A, B). This small effect (89% vs 92% of the major isomer) suggests that the hydroxymethyl group in the 2-position is not itself

Table 10. Alkylation of Methyl-Substituted Amides.[a]

Entry	Amide	Electrophile	Alkylation Conditions	Diastereomer Ratio[b]	Selectivity
A	15	CH_3CH_2I	25°C	92.0:8.0	11.5:1
B	36	CH_3CH_2I	25°C	88.9:11.1	8.0:1
C	38	CH_3CH_2I	25°C	94.6:5.4	17.5:1
D	40	CH_3CH_2I	25°C	75.6:24.4	3.1:1
E	15	CH_3CH_2I	4% HMPA/-100°C	90.7:9.3	9.8:1
F	38	CH_3CH_2I	5% HMPA/-100°C	91.6:8.4	10.9:1
G	40	CH_3CH_2I	5% HMPA/-100°C	78.0:22.0	4.0:1
H	33	CH_3CH_2I	-78°C	76.8:23.2	3.3:1
I	37	CH_3CH_2I	-78°C	92.4:7.6	12.2:1
J	39	CH_3CH_2I	-78°C	61.3:38.7	1.6:1
K	41	CH_3CH_2I	-78°C	98.5:1.5	66:1
L	33	i-C_4H_9I	-78°C	74.4:25.6	2.9:1
M	37	i-C_4H_9I	-78°C	75.4:24.6	3.1:1

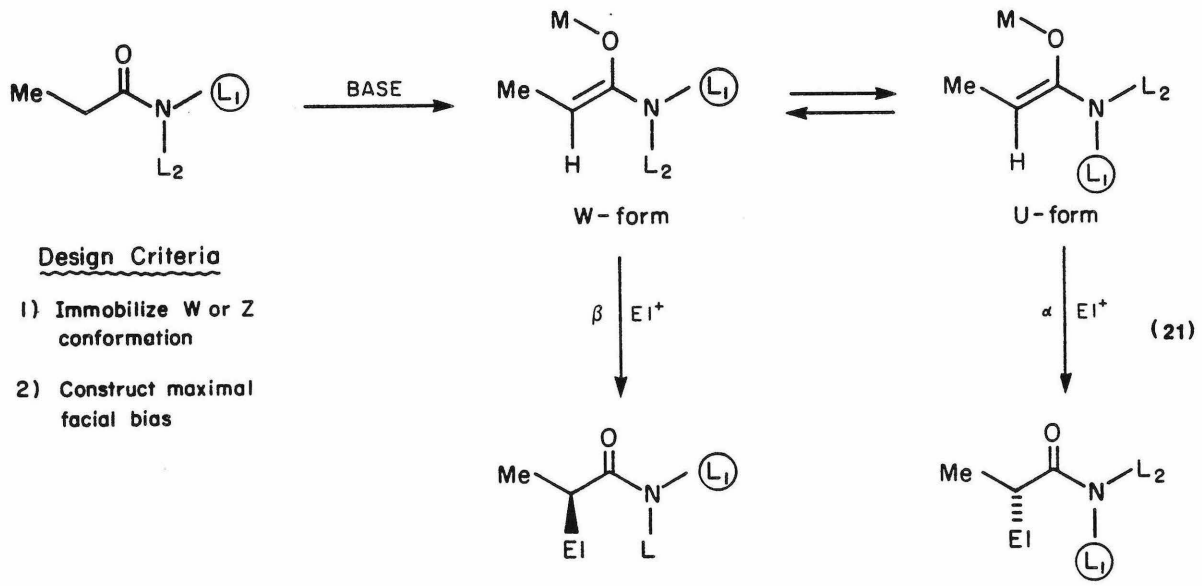
[a]Metallations performed by addition of amide to LDA in THF (25°C, 0.4 h).
[b]Diastereomer ratios determined by integration of peak areas on capillary VPC analysis (precision ±1%).

providing the steric bias but rather as in 42 (R_2 = R_3 = H, R_1 = CH_3) is out of the path of the incoming electrophile. Perhaps the 5-position of the ring is slightly tilted out of the planar array and oriented to provide the steric bias. Silylation of 36 gives the corresponding TBS-ether 37. The bisected transition state model 43 (R_1 = CH_3) predicts the geminal methyl groups must contribute the steric hindrance of the 3-position relative to the 5-position and hence block the α-face. Ethylation of the lithium enolate of 37 gives, as in the parent system, the opposite sense of diastereoselection relative to the dianion reaction. It also shows significantly improved selectivity (>12:1) relative to the parent TBS-ether 33 (3.3:1, Entries H, I).

Although somewhat more difficult to obtain, these geminally substituted amides may show some important practical advantages over the parent prolinol derived amides. Both the dimethyl and diphenyl derivatives indicate good chromatographic response which may be useful for the mechanical resolution of diastereomers in cases where even a few percent of a minor enantiomer cannot be tolerated. In addition, the diphenyl derivative upon simple ethylation gave a <u>solid</u> mixture of diastereomers. Disappointingly, the high selectivity observed in ethylation of TBS-ether 37 did not persist in reaction

with iso-butyl iodide (Entries L, M).

Considering structure 42 or as illustrated in equation 21, one would predict that an asymmetric center constrained in the U-form would be more effective in inducing selectivity than one constrained in the W-form.



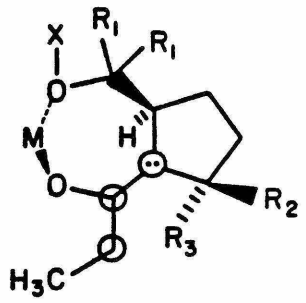
Further models 42 and 43 predict much different results depending on the relative stereochemistry between the hydroxymethyl group at C_2 and the substituent at C_5 (R_2 or R_3) of the pyrrolidine ring. We therefore examined the propionamides of cis- and trans-5-methyl-prolinol 38 and 40. The synthesis of 5-methylproline by Overberger and co-workers gives a mixture of cis and trans compounds from reduction of the intermediate

immium salt.[46] Isomer separation can be effected either by crystallization of the amino acids or chromatographically after reduction and acylation.[47] Although racemic materials were used in this study, both cis- and trans-5-methylproline have been resolved.[48] The cis and trans isomers were assigned in the literature on the basis of the CD spectra.

These alkylation results are also summarized in Table 10 (Scheme X). Recall the unsubstituted hydroxyamide shows diastereoselectivity of 11.5:1 (Entry A). The cis methyl group of hydroxyamide **38** reinforces the stereochemical bias of hydroxymethyl group in the 2-position to increase the overall selectivity to >17:1 (Entry B). Ethylation of the dianion derived from hydroxyamide **40** under identical conditions proceeds with the lowest observed preference in this series of substrates, only a 3.1:1 diastereoselection (Entry C). The trans methyl group as depicted in structure **42** ($R_1 = R_2 = H$, $R_3 = CH_3$) should oppose the induction of the hydroxymethyl side chain, while in this orientation, the cis methyl group, **42** ($R_1 = R_3 = H$, $R_2 = CH_3$), impedes approach from the same face. The reactions of the dilithio anions in the presence of HMPA show similar changes in selectivity.

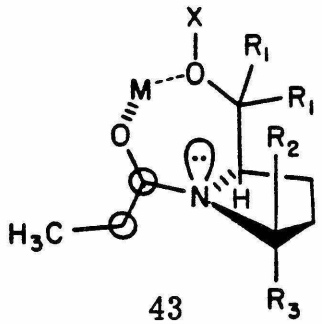
The corresponding silyl ethers, in which the parent selectivity from amide **33** is only 3.3:1 (Table 10, Entry H),

Scheme X



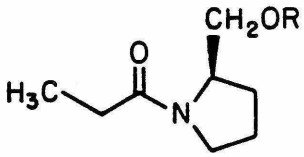
42

α- ATTACK FAVORED

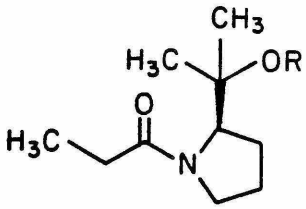


43

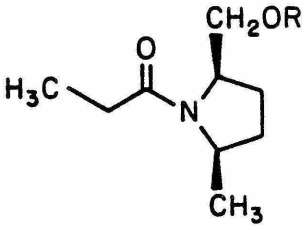
β- ATTACK FAVORED



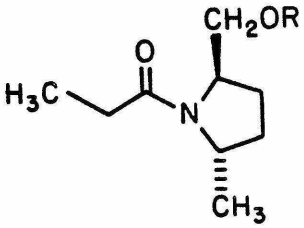
15	R = H	11.5 : 1
33	R = TBS	3.3 : 1



36	R = H	8.0 : 1
37	R = TBS	12.2 : 1



38	R = H	17.5 : 1
39	R = TBS	1.6 : 1



40	R = H	3.1 : 1
41	R = TBS	66 : 1

show the opposite trend. The cis-amide 39, which if the transition state more nearly resembles structure 43 (R_1 = R_3 = H, R_2 = CH_3) should be equally hindered on either side of the enolate. Reaction proceeds to give the same major diastereomer as amide 38 but in only a 61:39 ratio (1.6:1, Entry J). The trans-amide 41 again gives the corresponding diastereomer to the dianion alkylation of 40, but exhibits the highest diastereoselection (>50:1) observed for any ethylation (Entry K). In the model rotomer 43 (R_1 = R_2 = H, R_3 = CH_3) the methyl group would interact strongly with the reacting center.

These interesting experiments suggested by the simple chelation based models illustrated in equation 20 demonstrate a new design basis for chiral enolates focusing on the U-form (eq 21) of chirality disposition. The idea of subtle rotation about the C-N bond to accommodate the optimal chelation distance as a function of chelating group or, recalling the dipotassium and magnesium enolate experiments, the metal ion, provides a new basis for rationalizing the wide variations in the observed diastereoselection of seemingly similar systems.

III. Summary

In the study of prolinol derived amides discussed above we have systematically addressed the problems associated with diastereoselective alkylation as a practical approach to the control of acyclic stereochemistry. By proper choice of reaction conditions a seven-membered ring chelate can be utilized effectively in several different ways to induce high diastereoselection. The preparation of simple chiral carboxylic acids proceeds in good chemical yields and with the highest optical yields yet reported. From this study new standards have been set for both asymmetric induction and analysis of the asymmetric process. The work has defined new design concepts for the most effective orientation of chirality in chiral propionate enolates. These concepts and methods should find numerous application in the total synthesis of natural products.

IV. Experimental Section

Infrared spectra were recorded on a Beckmann 4210 spectrophotometer. ^{1}H magnetic resonance spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in ppm from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration, and interpretation. ^{13}C magnetic resonance spectra were recorded on a JEOL-FX-90Q (22.5 MHz) or a Varian Associates XL-100 (25.2 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Multiplicities are reported using the format given above. Mass spectra were recorded on a Dupont 21-492B spectrometer by the California Institute of Technology Microanalytical Laboratory. Combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan, or by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Analytical gas-liquid chromatography was carried out either on a Varian Aerograph Model 1400 gas chromatograph, equipped with a flame ionization detector, using a 10 ft x 0.125[11] in stainless steel column packed Superpak 20M Carbowax by Analabs or on a Hewlett Packard 5880A series

gas chromatograph equipped with a flame ionization detector, using a 25 m x 0.2 mm flexible fused silica capillary column wall-coated with Carbowax 20M or methyl silicone (SP-2100) or a 30 m x 0.32 mm fused silica capillary column wall-coated with SE-54. Silylations were performed using excess diethyltrimethylsilylamine.

Chromatography on silica was performed using a forced flow of the indicated solvent on Merck Silica Gel 60 (70-230 mesh). Medium pressure chromatography was performed using EM Laboratories LoBar silica gel 60 prepacked columns on a Chromatronic MPLC apparatus equipped with a Fluid Metering Inc. Model RP Lab Pump. Analytical HPLC was performed on a Water's Associates Model ALC 202/401 high pressure liquid chromatograph equipped with a Model 6000 pump and ultraviolet and refractive index detectors.

Optical rotations were recorded on a Perkin Elmer 141 polarimeter at the sodium D line or a Jasco DIP-181 digital polarimeter and are reported as follows: $[\alpha]_D$, concentration, c (g/100 mL), and solvent.[49]

Diethyl ether, tetrahydrofuran (THF), and dimethoxyethane (DME) were dried by distillation from benzophenone ketyl. Dichloromethane and alkyl iodides were passed through a column of activity I Alumina prior to use. Dimethylforamide (DMF) was distilled from calcium

hydride and hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride or sodium (triphenylmethane indicator) then stored over molecular sieves. Alkyllithiums were titrated by the procedure of Watson and Eastham.[50] Hydroxyamides were dried by bulb-to-bulb distillation (full pump or diffusion pump vacuum) and transferred to tared vials under nitrogen for weighting. All other reagents were used as received.

Unless otherwise noted all non-aqueous reactions were carried out under a nitrogen atmosphere with rigid exclusion of moisture from reagents and glassware.

General Acylation Procedure for the Preparation of Prolinol Derived Hydroxy-Amides. To 1.0 equiv of amino alcohol was added dropwise (exothermic) 1.1 equiv of anhydride with stirring. Upon complete addition the mixture was heated to ~70°C for 10 min. The mixture was cooled, basified with aqueous NaOH, and extracted with three portions of dichloromethane. The combined organics were washed with 10% aqueous HCl and brine, dried (Na_2SO_4) and concentrated in vacuo to yield hydroxy-amide which was evaporatively distilled prior to use.

1-[(2S)-Hydroxymethylpyrrolid-1-yl]-propionic Acid (15). Acylation of 23.9 g (0.24 mol) of (S)-prolinol with 34 mL (34.5 g, 0.26 mol) of propionic anhydride affords 32.3 g (86%) of 15 as a light amber oil. Bulb-to-bulb distillation (110°C,

<0.001 mm) affords 15 as a colorless liquid which crystallized on standing: mp 38-40°C; IR (neat) 3380, 2962, 2937, 2870, 1610, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (br s, 1, O$\underline{H}$), 4.20 (m, 1, CH), 3.67-3.39 (m, 4, N, O-$C\underline{H}_2$), 2.31 [q, J = 9 Hz, 2, C(O)-$C\underline{H}_2$], 2.13-1.58 (m, 4, $C\underline{H}_2$-$C\underline{H}_2$), 1.16 (t, J = 9 Hz, 3, -$C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 174.7 (s, $\underline{C}$=O), 66.9 (t, $\underline{C}H_2$-OH), 60.9 (d, $\underline{C}$H), 47.8 (t, $\underline{C}H_2$-N), 28.1 (t, $\underline{C}H_2$-$\underline{C}H_2$), 24.3 [t, C(O)-$\underline{C}H_2$), 8.9 (q, $\underline{C}H_3$); $[\alpha]_D$ = -65.3° ($\underline{c}$ 21.6, CH_2Cl_2).

Anal. calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.15; H, 9.65; N, 8.90.

1-[(2S)-Hydroxymethylpyrrolid-1-yl]-butanoic Acid (16). Acylation of 11.26 g (0.11 mol) of (S)-prolinol with 20 mL (19.34 g, 0.12 mol) of n-butyric anhydride affords 18.51 g of light amber oil. Bulb-to-bulb distillation (110°C, < 0.001 mm) affords 16 as a liquid: IR (neat) 3390, 2960, 2875, 1610 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.17 (t, J = 5 Hz, 1, O$\underline{H}$), 4.67-3.78 (m, 1, C$\underline{H}$), 3.77-3.28 (m, 4, N, O-$C\underline{H}_2$), 2.27 [t, J = 8 Hz, 2, C(O)$C\underline{H}_2$), 2.17-1.37 (m, 6, C-$C\underline{H}_2$-C), 0.97 (t, J = 7 Hz, 3, $C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 174.1 ($\underline{C}$=O), 66.9 ($\underline{C}H_2$OH), 60.8 ($\underline{C}$H), 48.0 (N-$\underline{C}H_2$), 36.9 (C-$\underline{C}H_2$-C), 28.2 (C-$\underline{C}H_2$-C, pyrrolidine), 24.3 (C-$\underline{C}H_2$-C, pyrrolidine), 18.1 [C(O)-$\underline{C}H_2$], 13.8 ($\underline{C}H_3$); $[\alpha]_D$ = -61.6° ($\underline{c}$ 16.6, CH_2Cl_2).

Anal. calcd. for $C_9H_{17}NO_2$: C, 63.12; H, 10.00; N, 8.18. Found: C, 63.05; H, 9.97; N, 8.26.

1-[(2S)-Hydroxymethylpyrrolid-1-yl]-acetic Acid (20).

Acylation of 4.97 g (4.9 mmol) of (S)-prolinol with 4.6 mL (4.98 g, 4.9 mmol) of acetic anhydride affords a mixture of hydroxy- and acetoxyamides. Chromatography on silica gel (ethyl acetate) afforded pure hydroxyamide 20: IR (neat) 3380, 2960, 2880, 1625, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.12 (t, J = 5 Hz, 1, O<u>H</u>), 4.28-3.78 (m, 1, N-C<u>H</u>), 3.78-3.28 (m, 4, N, O-C<u>H</u>$_2$), 2.17-1.56 (m, 4, C<u>H</u>$_2$), 2.07 (s, 3, C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 171.3 (<u>C</u>=O), 66.2 (<u>C</u>H$_2$OH), 60.6 (N-<u>C</u>H), 48.7 (N-<u>C</u>H$_2$), 28.0 (<u>C</u>H$_2$), 24.1 (<u>C</u>H$_2$), 22.8 (<u>C</u>H$_3$).

<u>Anal</u>. calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15. Found: C, 58.56; H, 9.05.

<u>General Procedures for the Enantioselective Alkylations of Chiral Hydroxy-Amide Derivatives.</u> <u>Preparation of Lithium Diisopropylamide (LDA)</u>. To a cooled (0°C) solution of 1.2-1.5 equiv of diisopropylamine in THF (0.1-0.5 <u>M</u>) was added 1.0 equiv of <u>n</u>-butyllithium in hexanes with stirring. Upon complete addition, the mixture was warmed to room temperature and used as a standard solution.

<u>Preparation of "Hexane-Free" LDA</u>. Concentration of a standard solution of LDA (prepared as above) <u>in vacuo</u> afforded a white solid. Addition of THF gave a standard solution of "hexane-free" LDA.

<u>Lithium Enolate Alkylation Conditions</u>. To a stirred

solution of 2.1 equiv (1.1 equiv for O-alkyl amides) of LDA in THF (or indicated solvent, 0.1-0.5 M) was added 1.0 equiv of amide. The resulting solution was stirred at room temperature for 10-30 min, followed by the addition of 2.1 equiv of the appropriate complexing agent. The mixture was cooled to the desired alkylation temperature and 1.0-1.5 equiv of alkyl halide added dropwise, at a rate to maintain the desired temperature. The reaction mixture was stirred 3-12 h.

Mixed Metal Enolate Alkylation Conditions. A slurry of 1.2-1.5 equiv of alkali metal hydride in mineral oil was washed with four portions of pentane to remove the oil. To the residue was added a sufficient volume of THF to yield a 0.1-0.5 M solution upon addition of 1.0 equiv of hydroxy-amide. Upon cessation of gas evolution, 1.05-1.1 equiv of LDA was added. The resulting mixture was stirred at room temperature for 10-30 min. Following the addition of 2.1 equiv of the appropriate complexing agent, the reaction mixture was cooled to the desired alkylation temperature and 1.0-1.2 equiv of alkyl halide added dropwise, at a rate to maintain the desired temperature. The reaction mixture was stirred 3-6 h.

Standard Isolation Procedure. The resulting reaction mixtures were quenched by dropwise addition of saturated

aqueous ammonium chloride or water. This mixture was partitioned between solvent and water or brine then the aqueous layer extracted with 1-3 portions of the indicated solvent. The combined organic extracts were dried (Na_2SO_4 or $MgSO_4$) and concentrated *in vacuo* to afford the alkylation product.

General Procedure for the Acidic Hydrolysis of Hydroxy-Amide Derivatives. To 4-5 equiv of 1.0 *N* HCl was added 1.0 equiv of amide. The resulting vigorously stirred mixture was heated to reflux for 2-3 h then cooled and basified with aqueous NaOH. The resulting solution was extracted with two portions of methylene chloride. The aqueous layer was acidified with 1.0 *N* HCl and extracted with two portions of ether. These latter combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford the carboxylic acid.

(2R)-1-[(2S)-2-Hydroxymethyl-pyrrolid-1-yl]-2-methyl-1-butanoic Acid (28, Table 2, Entry A). To a solution (25°C) of lithium enolate derived from 366 mg (2.3 mmol) of hydroxy amide **15** in THF was added 200 μL (390 mg, 2.5 mmol) of ethyl iodide. After 6 h at room temperature the mixture was quenched with water. The standard isolation procedure (methylene chloride) afforded 421 mg (98%) of **28** as a yellow oil: IR (CCl_4) 3315, 2975, 2890, 1605, 1470, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 (t, J = 4

Hz, 1, O$\underline{H}$), 4.22 (m, 1, N-C$\underline{H}$), 3.78-3.22 (m, 4, N, O-C$\underline{H}_2$), 2.47 [m (t of q), J = 7 Hz, 1, C(O)-C$\underline{H}$], 2.22-1.22 (m, 6, C-C$\underline{H}_2$-C), 1.13 (d, J = 7 Hz, 3, CH-C$\underline{H}_3$), 0.89 (t, J = 7 Hz, 3, CH_2-C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 177.64 (s, $\underline{C}$=O), 66.15 (t, $\underline{C}H_2OH$), 60.46 (d, N-$\underline{C}$H), 47.78 (t, N-$\underline{C}H_2$), 39.66 [d, C(O)-$\underline{C}$H), 27.95 (t, C-$\underline{C}H_2$-C), 26.65 [t, (R)-$\underline{C}H_2$-CH_3), 24.32 (t, C-$\underline{C}H_2$-C), 17.28 [q, 92%, (R)-CH-$\underline{C}H_3$), 16.57 [q, 8%, (S)-CH-$\underline{C}H_3$-], 11.97 (q, CH_2-$\underline{C}H_3$). VPC analysis (25 m Carbowax, 165°C) showed two peaks at 9.81 (92.0%) and 10.10 min (8.0%).

Anal. calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.73; H, 10.32; N, 7.52.

An authentic mixture of **28** and **29** was prepared by enolization of a sample of **28** with LDA (THF, 25°C, 15 min) followed by reprotonation with ammonium chloride. The isolation procedure (methylene chloride) afforded **28** and **29** as an amber oil: ^{13}C NMR ($CDCl_3$) δ 177.95 ($\underline{C}$=O), 67.52 ($\underline{C}H_2$-OH), 61.09 [(S)-N-$\underline{C}$H), 60.90 [(R)-N-$\underline{C}$H], 47.90 (N-CH_2), 39.70 [C(O)-$\underline{C}$H], 28.23 (C-$\underline{C}H_2$-C), 27.28 [(S)-$\underline{C}H_2$-CH_3), 26.56 [(R)-$\underline{C}H_2$-CH_3), 24.41 (C-$\underline{C}H_2$-C), 17.23 [(R)-CH-$\underline{C}H_3$), 16.52 [(S)-CH-$\underline{C}H_3$], 11.95 (CH_2-$\underline{C}H_3$).

(R)-2-Methylbutanoic Acid (Table 2, Entry A). Hydrolysis of 421 mg (2.27 mmol) of amide **28** in 8.0 mL of 1.0 N HCl gave after bulb-to-bulb distillation 196 mg (84%) of 2-methylbutanoic acid: $[\alpha]_D$ = -15.95°

(neat). Lit.[51] $[\alpha]_D$ = +19.6° (neat).

(2R)-1-[(2S)-2-Hydroxymethyl-pyrrolid-1-yl]-2-methyl-1-hexanoic Acid (44, Table 2, Entry B). To a solution (25°C) of lithium enolate derived from 1.486 g (9.46 mmol) of hydroxy-amide 15 was added 1.2 mL (1.94 g, 10.5 mmol) of n-butyl iodide. After 6 h (25°C), the mixture was quenched with water. The standard isolation procedure (methylene chloride) gave 2.031 g (100%) of 44 as a yellow liquid: IR (neat) 3400, 2965, 2945, 2885, 1640 (sh), 1620, 1470, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (br t, 1, O$\underline{H}$), 4.22 (m, 1, N-C$\underline{H}$), 3.78-3.22 (m, 4, N, O-C$\underline{H}_2$), 2.56 [m, 1, C(O)-C$\underline{H}$], 2.22-1.0 (m, 10, C-$\underline{C}H_2$-C), 1.13 (d, J = 7 Hz, 3, CH-C$\underline{H}_3$), 0.89 (br t, J = 6 Hz, 3, CH_2-C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 177.7 ($\underline{C}$=O), 66.1 ($\underline{C}H_2OH$), 60.4 (N-$\underline{C}H$), 47.8 (N-$\underline{C}H_2$), 38.0 [C(O)$\underline{C}H$], 33.4 ($\underline{C}H_2$-CH-CH_3), 29.7 ($\underline{C}H_2$), 28.0 ($\underline{C}H_2$), 24.3 ($\underline{C}H_2$), 22.8 ($\underline{C}H_2$), 17.7 [94%, (R)-CH-$\underline{C}H_3$), 16.9 [6%, (S)-CH-$\underline{C}H_3$], 14.0 (CH_2-$\underline{C}H_3$); $[\alpha]_D$ = -69.5° (c 3.4, CH_2Cl_2). VPC analysis (-OTMS derivative, 25 m Me-Si, 145°C) shows two peaks at 22.55 min (5.8%) and 23.05 min (94.2%).

Anal. calcd. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87. Found: C, 67.49; H, 10.96.

An authentic diastereomeric mixture (2R,2S) of 1-[(2S)-2-hydroxymethyl-pyrrolid-1-yl]-2-methyl-1-

hexanoic acid was prepared by enolization of a sample of 2R-amide 44 with LDA (THF, 25°C, 15 min) followed by reprotonation with ammonium chloride. The standard isolation procedure (methylene chloride) afforded a mixture of diastereomers as an amber oil: ^{13}C NMR ($CDCl_3$) δ 178.4 (C=O), 67.8 (CH_2-OH), 61.3 (N-CH), 61.1 (N-CH), 48.0 (N-CH_2), 47.9 (N-CH_2), 38.2 [C(O)-CH], 34.1 [(S)-CH_2-CH-CH_3], 33.4 [(R)-CH_2-CH-CH_3), 29.8 (CH_2), 29.6 (CH_2), 28.3 (CH_2), 24.5 (CH_2), 22.8 (CH_2), 17.7 [(R)-CH-CH_3), 16.9 [(S)-CH-CH_3), 14.0 (CH_2-CH_3).

(R)-2-Methylhexanoic Acid (Table 2, Entry B). Hydrolysis of 388 mg (1.82 mmol) of 44 in 7 mL of 1.0 N HCl afforded after bulb-to-bulb distillation 184 mg (78%) of 2-methylhexanoic acid: $[\alpha]_D$ = -16.71° (neat). Lit.[52] $[\alpha]_D$ = +18.7° (neat).

(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2-methyl decanoic Acid (45, Table 2, Entry C).[5e] To a cooled (-78°C) solution of mixed lithium-potassium enolate derived from 397 mg (2.53 mmol) of hydroxy-amide 15 in THF-HMPA was added 0.51 mL (0.67 g, 2.78 mmol) of n-octyl iodide as a 50% THF solution. The mixture was stirred at -78°C for 6 h then quenched with saturated ammonium chloride. The standard isolation procedure (ether) afforded after chromatography on silica gel (150 g, ethyl acetate) 533 mg (78%) of amide 45 as a colorless

liquid: IR (neat) 3400, 2965, 2938, 2862, 1645 (sh), 1618, 1468, 1442 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.17 (br s, 1, O<u>H</u>), 4.17 (m, 1, N-C<u>H</u>), 3.7-3.37 (m, 4, N, O-C<u>H</u>$_2$), 2.54 [m, 1, C(O)-C<u>H</u>], 2.17-0.73 (m, 24, C<u>H</u>$_2$, C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 178.2 (<u>C</u>=O), 67.2 (<u>C</u>H$_2$OH), 60.9 (N-<u>C</u>H), 47.9 (N-<u>C</u>H$_2$), 38.1 [C(O)-<u>C</u>H), 33.7 [C(O)-CH-<u>C</u>H$_2$], 31.8 (<u>C</u>H$_2$), 29.7 (<u>C</u>H$_2$), 29.5 (<u>C</u>H$_2$), 29.3 (<u>C</u>H$_2$), 28.2 (<u>C</u>H$_2$), 27.6 (<u>C</u>H$_2$), 24.4 (<u>C</u>H$_2$), 22.6 (<u>C</u>H$_2$), 17.7 (CH-<u>C</u>H$_3$), 14.1 (CH-<u>C</u>H$_3$); $[\alpha]_D$ = -55.6° (<u>c</u> 2.8, CH_2Cl_2) shows two peaks at 20.92 (5.5%) and 21.87 min (94.5%).

<u>Anal</u>. calcd. for $C_{16}H_{31}NO_2$: C, 71.33; H, 11.60. Found: C, 71.29; H, 11.70.

<u>(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2,4-dimethyl-1-pentanoic Acid (12, Table 2, Entry D)</u>. To a cooled (-100°C) solution of lithium enolate derived from 3.129 g (19.9 mmol) of hydroxy-amide <u>15</u> in THF-HMPA was added 2.54 mL (4.04 g, 2.19 mmol) of <u>iso</u>-butyl iodide. The reaction mixture was slowly warmed to -40°C over 10 h, then quenched with water. The standard isolation procedure, partitioning between ether-brine and extraction with three portions of methylene chloride, afforded after chromatography on silica gel (250 g, ethyl acetate) 3.56 g (84%) of amide <u>12</u> as a clear liquid: IR (neat) 3390, 2955, 2930 (sh), 2865, 1630 (sh), 1610, 1458, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.16 (br t, 1, O<u>H</u>), 4.20

(m, 1, N-C$\underline{H}$), 3.78-3.33 (m, 4, N, O-C$\underline{H}_2$), 2.53 [m, 1, C(O)-C$\underline{H}$], 2.22-1.00 (m, 7, C-C$\underline{H}_2$-C, CH_3-C$\underline{H}$-CH_3), 1.19 [d, J = 7 Hz, 3, C(O)-CH-C$\underline{H}_3$], 0.89 (d, J = 6 Hz, 6, C$\underline{H}_3$-CH-C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 178.2 ($\underline{C}$=O), 67.1 ($\underline{C}H_2OH$), 60.8 (n-$\underline{C}$H), 47.8 (N-$\underline{C}H_2$), 42.7 [C(O)-CH-$\underline{C}H_2$], 36.1 [C(O)-$\underline{C}$H], 28.2 ($\underline{C}H_2$), 25.9 (CH_3-$\underline{C}$H-CH_3), 24.5 ($\underline{C}H_2$), 23.0 ($\underline{C}H_3$-CH-CH_3), 22.4 (CH_3-CH-$\underline{C}H_3$), 17.8 [97%, (R)C(O)-$\underline{C}$H-CH_3], 17.1 [3%, (S)C(O)-$\underline{C}$H-CH_3]; $[\alpha]_D$ (diastereomer ratio 97.4:2.6) = -66.6° ($\underline{c}$ 12.6, CH_2Cl_2). VPC analysis (25 m methyl silicone, 150°C) shows two peaks at 12.94 (2.4%) and 13.42 min (97.6%).

Anal. calcd. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.47; H, 10.91; N, 6.71.

An authentic diastereomeric mixture of **12** and the C_2-epimer **46** was prepared by enolization of a sample of **12** with LDA (THF, 25°C, 45 min) followed by reprotonation with water. The standard isolation procedure (methylene chloride) afforded a mixture of diastereomers as an amber oil: ^{13}C NMR ($CDCl_3$) δ 177.8 ($\underline{C}$=O), 66.4 ($\underline{C}H_2$-OH), 60.8 (N-$\underline{C}$H), 47.8 (N-$\underline{C}H_2$), 43.4 [(S)C(O)-CH-$\underline{C}H_2$], 42.6 [(R)C(O)-CH-$\underline{C}H_2$], 36.0 [C(O)-$\underline{C}$H), 28.0 ($\underline{C}H_2$), 25.9 (CH_3-$\underline{C}$H-CH_3), 24.4 ($\underline{C}H_2$), 22.9 ($\underline{C}H_3$-CH-CH_3), 22.6 (CH_3-CH-$\underline{C}H_3$), 17.7 [(R)C(O)-CH-$\underline{C}H_3$], 17.1 [(S)C(O)-CH-$\underline{C}H_3$].

(2R)-2,4-Dimethyl-1-pentanoic Acid (Table 2, Entry D).

Hydrolysis of 3.36 g (15.8 mmol) of amide 12 in 100 mL of 1.0 N HCl afforded after bulb-to-bulb distillation 1.96 g (96%) of 2,4-dimethyl pentanoic acid: $[\alpha]_D$ = -18.97° (neat); $[\alpha]_D$ = -21.9° (c 5.39, ether). Lit.[53] $[\alpha]_D$ = +19.4° (c 5.23, ether).

(2R,4S)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-5-benzyloxy-2,4-dimethyl-pentanoic Acid (47, Table 2, Entry E). To a cooled (-100°C) solution of lithium enolate derived from 3.132 g(19.9 mmol) of hydroxyamide 15 in THF-HMPA was added 6.0 g (20.7 mmol) of (R)-3-benzyloxy-2-methylpropyl iodide 54 as a 50% THF solution.[54] The mixture was slowly warmed to -40°C over 12 h, then quenched with saturated ammonium chloride. The standard isolation procedure (ether) afforded after chromatography on silica gel (350 g, ethyl acetate) 3.768 g (59%) of amide 47 as a pale yellow oil: IR (neat) 3410, 3100, 3075, 3040, 2975, 2945, 2880, 1642 (sh), 1618, 1492, 1468, 1460, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (s, 5, Ar), 5.17 (br s, 1, O<u>H</u>), 4.47 (s, 2, Ar-C<u>H</u>$_2$), 3.50 (m, 1, N-C<u>H</u>), 3.67-3.23 (m, 6, N, O-C<u>H</u>$_2$), 2.70 [m, 1, C(O)-C<u>H</u>], 2.06-1.33 (m, C<u>H</u>$_2$, OCH$_2$-C<u>H</u>-CH$_3$), 1.10 [d, J = 7 Hz, 3, C(O)-CH-C<u>H</u>$_3$], 0.93 (d, J = 7 Hz, 3, OCH$_2$-CH-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 178.1 (<u>C</u>=O), 138.5 (Ar), 128.2 (Ar), 127.6 (Ar), 127.5 (Ar), 76.2 (Ar-<u>C</u>H$_2$), 73.1 (ArCH$_2$O-<u>C</u>H$_2$), 67.1 (<u>C</u>H$_2$OH), 60.8 (N-<u>C</u>H), 47.5 (N-<u>C</u>H$_2$), 38.0 [C(O)-CH-<u>C</u>H$_2$], 35.7

[C(O)-$\underline{C}$H-CH_3], 31.5 (OCH_2-$\underline{C}$H-CH_3), 28.0 ($\underline{C}H_2$), 24.3 ($\underline{C}H_2$), 17.8 ($\underline{C}H_3$), 17.6 ($\underline{C}H_3$); $[\alpha]_D$ (diastereomer ratio, 1.7:95.5:2.8) = -50.5° (*c* 4.4, CH_2Cl_2). VPC analysis (25 m Methyl Silicone, 180°C) showed peaks at 39.79 [(2S,4S), 1.8%], 40.83 [(2R,4S), 95.5%] and 41.42 min [(2R,4R), 2.7%].

Anal. calcd. for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15. Found: C, 71.29; H, 9.10.

(2R,4S)-5-Benzyloxy-2,4-dimethylpentanoic Acid (48, Table 3, Entry E). Hydrolysis of 537 mg (1.68 mmol) of amide **47** in 15 mL of 1.0 *N* HCl gave 363 mg (91%) of carboxylic acid **48**: IR (neat) 3450-2350, 1732 (sh), 1705, 1603, 1493, 1463 (sh), 1452 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.48 (br s, 1, $CO_2\underline{H}$), 7.30 (s, 5, Ar), 4.44 (s, 2, Ar-$\underline{C}H_2OCH_2$), 3.24 (d, J = 5 Hz, 2, $ArCH_2O\underline{C}H_2$), 2.52 [m, 1, C(O)-$\underline{C}$H], 1.79 (m, 1, OCH_2-$\underline{C}$H), 1.50 (overlapping d's, J = 7 Hz, 2, CH-$\underline{C}H_2$-CH), 1.12 [d, J = 7.5 Hz, 3, C(O)CH-$\underline{C}H_3$], 0.93 (d, J = 7 Hz, 3, OCH_2-CH-$\underline{C}H_3$).

(2R,4R)-1-[(2S)-2-Hydroxylmethylpyrrolid-1-yl]-5-benzyloxy-2,4-dimethylpentanoic Acid (49, Table 2, Entry F).[55] To a cooled (-78°C) solution of mixed lithium-potassium enolate derived from 5.869 g (37.4 mmol) of hydroxy amide **15** in THF-HMPA was added 11.3 g (39.0 mmol) of (S)-3-benzyloxyl-2-methylpropyl iodide[54] as a 50% THF solution. The mixture was stirred at -78°C for 6 h,

then quenched with saturated ammonium chloride solution. The standard isolation procedure (hexane) afforded after chromatography on silica gel (300 g, ethyl acetate) 9.261 g (78%) of amide 49 as a colorless oil: IR (neat) 3400, 3070, 3035, 2985, 2940, 2880, 1640 (sh), 1617, 1480 (sh), 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (s, 5, Ar), 5.12 (br s, 1, O<u>H</u>), 4.44 (s, 2, Ar<u>CH_2</u>O), 4.14 (m, 1, N-<u>CH</u>), 3.67-3.24 (m, 4, N, O-<u>CH_2</u>), 3.29 (d, J = 5 Hz, 2, $ArCH_2O$<u>CH_2</u>), 2.68 [m, 1, C(O)<u>CH</u>], 2.09-1.44 (m, 6, <u>CH_2</u>), 1.44-1.0 (m, 1, OCH_2-<u>CH</u>), 1.12 [d, J = 7 Hz, 3, C(O)-CH-<u>CH_3</u>], 0.96 (d, J = 6.5 Hz, 3, OCH_2-CH-<u>CH_3</u>); ^{13}C NMR ($CDCl_3$) δ 178.0 (<u>C</u>=O), 138.6 (Ar), 128.2 (Ar), 127.6 (Ar), 127.5 (Ar), 75.7 (Ar<u>CH_2</u>), 73.0 ($ArCH_2O$<u>CH_2</u>), 67.3 (<u>CH_2</u>OH), 60.9 (N-<u>C</u>H), 47.6 (N-<u>CH_2</u>), 37.8 (HC-<u>CH_2</u>-CH), 35.8 [C(O)-<u>C</u>H], 31.4 (OCH_2-<u>C</u>H), 28.1 (<u>CH_2</u>), 24.3 (<u>CH_2</u>), 18.0 (overlapping <u>CH_3</u>); $[\alpha]_D$ = -50.0° (<u>c</u> 5.2, CH_2Cl_2). VPC analysis (15 m Carbowax, 210°C) showed peaks at 28.14 [(2S,4R), 1.8%], 27.36 [(2R,4S), 5.2%] and 28.87 min [(2R,4R), 92.9%].

<u>Anal</u>. calcd. for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15. Found: C, 71.48; H, 9.07.

<u>(2R,4R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2,4-dimethylhept-6-enoic Acid (50, Table 2, Entry G)</u>. To a cooled (-78°C) solution of mixed lithium-potassium enolate derived from 2.711 g (17.3 mmol) of hydroxy-amide 15 in THF-HMPA was added 3.89 g (18.5 mmol) of (R)-1-

iodo-2-methyl-4-pentene[56] as a 50% THF solution. The mixture was stirred at -78°C for 6 h, then quenched with saturated ammonium chloride. The standard isolation procedure, partitioning between hexane-brine and extraction with two portions of ether, afforded after chromatography on silica gel (300 g, ethyl acetate) 2.135 g (52%) of amide 50 as a yellow liquid: IR (neat) 3400, 3082, 2970, 2940, 2920, 2880, 1640 (sh), 1620, 1460, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.03-5.53 (m, 1, C=C<u>H</u>), 5.23-4.83 (m, 2, <u>H</u>$_2$C=C), 4.22 (m, 1, N-C<u>H</u>), 3.73-3.37 (m, 4, N, O-C<u>H</u>$_2$), 2.69 [m, 1, C(O)-C<u>H</u>], 2.22-1.0 (m, 9, C<u>H</u>, C<u>H</u>$_2$), 1.13 [d, J = 7 Hz, 3, C(O)-CH-C<u>H</u>$_3$), 0.87 (d, J = 6 Hz, 3, C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 178.0 (<u>C</u>=O), 136.9 (H_2C=<u>C</u>H), 115.9 (<u>C</u>H$_2$=CH), 67.2 (<u>C</u>H$_2$-OH), 60.8 (N-<u>C</u>H), 47.8 (N-<u>C</u>H$_2$), 41.3 (CH-<u>C</u>H$_2$), 40.5 (CH-<u>C</u>H$_2$), 35.7 [C(O)-<u>C</u>H], 30.4 (CH_2-<u>C</u>H-CH_2), 28.1 (<u>C</u>H$_2$), 24.4 (<u>C</u>H$_2$), 19.7 (CH_3), 18.2 [C(O)-CH-<u>C</u>H$_3$]; $[\alpha]_D$ (diastereomer ratio, 91.9:2.8:5.3) = -67.2° (<u>c</u> 3.59, CH_2Cl_2). VPC analysis (50 m Carbowax, 175°C) showed peaks at 38.71 [(2R,4R), 91.3%], 39.12 [(2S,4R), 3.0%], and 39.71 min [(2R,4S), 5.7%].

<u>Anal</u>. calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53. Found: C, 69.31; H, 10.43.

An authentic diastereomeric mixture (2R,2S) of amide 50 was prepared by enolization of a sample of 2R-amide with LDA (THF, 25°C, 15 min) followed by reprotonation

with ammonium chloride solution. The standard isolation procedure (methylene chloride) afforded a mixture of diastereomeric amides as an amber liquid: ^{13}C NMR ($CDCl_3$) δ 178.0, 136.9, 115.9, 67.1, 61.0, 60.8, 47.8, 41.5, 41.3, 40.9, 40.5, 35.9, 35.7, 30.7, 30.5, 28.1, 24.4, 19.8, 19.5, 18.3 [(R), C(O)-CH-$\underline{C}H_3$], 16.8 [(S), C(O)-CH$\underline{C}H_3$].

(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2-methylpent-4-enoic Acid (51, Table 2, Entry H). To a cooled (-100°C) solution of lithium enolate derived from 6.88 g (43.8 mmol) of hydroxy-amide 15 in THF-HMPA was added 4.2 mL (5.87 g, 48.5 mmol) of allyl bromide. The reaction mixture was slowly warmed to -70°C over 6 h, then quenched with saturated ammonium chloride solution. The standard isolation procedure, partitioning between ether-brine and extraction with three portions of methylene chloride, afforded after chromatography on silica gel (350 g, ethyl acetate) 8.50 g (98%) of amide 51 as a pale yellow liquid: IR ($CHCl_3$) 3350, 3075, 2975, 2875, 1615 (sh), 1605, 1457, 1435, 1330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.11-5.50 (m, 1, H_2C=C$\underline{H}$), 5.20-4.87 (m, 3, $\underline{H}_2C$=CH, O$\underline{H}$), 4.19 (m, 1, N-C$\underline{H}$), 3.73-3.28 (m, 4, N, O-C$\underline{H}_2$), 2.83-1.50 [m, 7, C(O)-C$\underline{H}$], C-C$\underline{H}_2$-C], 1.16 (d, J = 7 Hz, 3, CH-C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 177.1 ($\underline{C}$=O), 136.0 (H_2C=$\underline{C}$H), 116.6 (H_2C=$\underline{C}$H), 66.8 ($\underline{C}H_2OH$), 60.8 (N-$\underline{C}$H), 47.8 (N-$\underline{C}H_2$), 38.1

[C(O)-$\underline{C}$H-$\underline{C}H_2$], 37.8 [C(O)-$\underline{C}$H-$\underline{C}H_2$], 28.2 ($\underline{C}H_2$), 24.4 ($\underline{C}H_2$), 17.3 [96%, (R)-CH-$\underline{C}H_3$), 16.6 [4%, (S)-CH-$\underline{C}H_3$]; $[\alpha]_D$ (diastereomer ratio 96.5:3.5) = -84.9° (c 15.27, CH_2Cl_2). VPC analysis (-OTMS derivative, 50 m Carbowax, 190°C) shows two peaks at 5.62 (96.2%) and 5.71 min (3.8%).

Anal. calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 67.22; H, 9.51.

(R)-2-Methyl-1-pent-4-enoic Acid (Table 2, Entry H). Hydrolysis of 8.49 g (43.1 mmol) of amide 51 in 220 mL of 1.0 N HCl afforded 4.39 g (89%) of 2-methyl-1-pent-4-enoic acid: $[\alpha]_D$ = -7.62° (neat).[57] Lit.[58] $[\alpha]_D$ = +8.24° (neat).

(2R)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2-methyl-3-phenylpropionic Acid (52, Table 2, Entry I). To a solution (25°C) of lithium enolate derived from 1.498 g (9.54 mmol) of hydroxy-amide 15 in THF was added 1.25 mL (1.80 g, 10.5 mmol) of benzyl bromide. After 6 h at 25°C the reaction mixture was quenched with water. The standard isolation procedure, partitioning between ether-brine and extraction with two portions of methyl chloride, afforded after chromatography on silica gel (EtOAc) 1.760 g (75%) of amide 52 as a pale yellow liquid: IR (neat) 3400, 3095, 3060, 3035, 2975, 2940, 2880, 1638 (sh), 1617, 1485, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ

7.21 (br s, 5, Ar), 5.17 (br s, 1, O$\underline{H}$), 4.09 (br m, 1, N-C$\underline{H}$), 3.67-2.50 [m, 7, Ar, N, O-C$\underline{H}_2$), C(O)-C$\underline{H}$], 2.0-1.33 (m, 4, C-C$\underline{H}_2$-C), 1.17 (overlapping d's, J = 6 Hz, 3, CH-C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 1-7.0 ($\underline{C}$=O), 139.7 (Ar), 128.9 (Ar), 128.3 (Ar), 126.3 (Ar), 66.6 ($\underline{C}H_2OH$), 60.6 (N-$\underline{C}$H), 47.7 (N-$\underline{C}H_2$), 40.5 [overlapping C(O)-$\underline{C}$H-$\underline{C}H_2$], 27.8 ($\underline{C}H_2$), 24.0 ($\underline{C}H_2$), 17.9 [(R)-CH-$\underline{C}H_3$], 17.2 [(S)-CH-$\underline{C}H_3$]; $[\alpha]_D$ (diastereomer ratio 89.9:10.1) = -102.5° ($\underline{c}$ 3.0, CH_2Cl_2). VPC analysis (-OTMS derivative, 25 m methyldilicone, 195°C) shows two peaks at 8.49 (87.6%) and 8.68 min (12.4%).

<u>Anal</u>. calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.88; H, 8.63; N, 5.70.

An authentic diastereomeric mixture (2R,2S) of 1-[(2S)-2-hydroxymethylpyrrolid-1-yl]-2-methyl-3-phenylpropionic acid was prepared by enolization of a sample amide 52 with LDA (THF, 0°C, 40 min) followed by reprotonation with ammonium chloride. The standard isolation procedure (methylene chloride) afforded a mixture of diastereomers as an amber oil: ^{13}C NMR ($CDCl_3$) δ 177.1 (s, $\underline{C}$=O), 139.5 (s, Ar), 128.8 (d, Ar), 128.7 (d, Ar), 128.1 (d, Ar), 126.2 (d, Ar), 67.2 (t, $\underline{C}H_2$-OH), 66.9 (t, $\underline{C}H_2$-OH), 61.1 (d, N-$\underline{C}$H), 60.8 (d, N-$\underline{C}$H), 47.7 (t, N-$\underline{C}H_2$), 41.1 [C(O)-$\underline{C}$H-$\underline{C}H_2$], 40.7 [C(O)-$\underline{C}$H-$\underline{C}H_2$], 40.5 [C(O)-$\underline{C}$H-$\underline{C}H_2$], 28.1 (t, $\underline{C}H_2$), 28.0 (t, $\underline{C}H_2$), 24.3 (t, $\underline{C}H_2$),

24.1 (t, $\underline{C}H_2$), 17.9 [q, (R)-CH-$\underline{C}H_3$], 17.2 [q, (S)-CH-$\underline{C}H_3$].

(R)-2-Methyl-3-phenylpropionic Acid (Table 2, Entry I). Hydrolysis of 1.663 g (6.7 mmol) of amide 52 in 35 mL of 1.0 N HCl afforded 1.02 g (92%) of 2-methyl-3-phenylpropionic acid: $[\alpha]_D$ = -18.9° (neat).[57] Lit.[59] $[\alpha]_D$ = -25.2° (neat).

(2S)-1-[(2S)-2-Hydroxymethyl-pyrrolid-1-yl]-2-methyl-1-butanoic Acid (29, Table 2, Entry J). To a cooled (-100°C) solution of lithium enolate derived from 2.128 g (12.4 mmol) of hydroxy-amide 16 in THF-HMPA was added 0.85 mL (1.94 g, 13.6 mmol) of methyl iodide. The stirred mixture was slowly warmed to -30°C over 12 h, then quenched with saturated ammonium chloride solution. The standard isolation procedure, partitioning between ether-brine and extraction with three portions of methylene chloride, afforded after filtration through silica gel (200 g, ethyl acetate) 2.268 g (98%) of amide 29 as a yellow oil: IR (neat) 3390, 2960, 2935, 2875, 1630 (sh), 1610, 1460, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (br t, 1, O$\underline{H}$), 4.16 (m, 1, N-C$\underline{H}$), 3.72-3.22 (m, 4, N, O-C$\underline{H}_2$), 2.44 [m, 1, C(O)-C$\underline{H}$], 2.11-1.22 (m, 6, C-C$\underline{H}_2$-C), 1.09 (d, J = 7 Hz, 3, CH-C$\underline{H}_3$), 0.90 (t, J = 7 Hz, 3, CH_2-C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 177.7 ($\underline{C}$=O), 67.4 ($\underline{C}H_2$-OH), 61.0 (N-$\underline{C}$H), 47.9 (N-$\underline{C}H_2$), 39.6 [C(O)-$\underline{C}$H], 28.1 ($\underline{C}H_2$), 27.2 [94%, (S)-CH-$\underline{C}H_2$], 26.5 [6%, (R)-CH-$\underline{C}H_2$], 24.3 ($\underline{C}H_2$),

16.5 (CH-$\underline{C}H_3$), 11.7 (CH_2-$\underline{C}H_3$); $[\alpha]_D$ (diastereomer ratio = 94.8:5.2) = -27.32° (*c* 9.8, CH_2Cl_2). VPC analysis (25 m Carbowax, 160°C) shows two peaks at 11.87 (5.8%) and 12.44 min (94.2%).

Anal. calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34. Found: C, 64.91; H, 10.39.

(S)-2-Methylbutanoic Acid. Hydrolysis of 2.09 g (11.3 mmol) of amide **29** in 60 mL of 1.0 *N* HCl afforded after bulb-to-bulb distillation 1.11 g (96%) of 2-methylbutanoic acid: $[\alpha]_D$ = +17.0° (neat). Lit.[51] $[\alpha]_D$ = +19.6° (neat).

1-[2-Hydroxymethylpyrrolid-1-yl]-4-methylpentanoic Acid (18). To a solution (25°C) of lithium enolate derived from 913 mg (6.4 mmol) of hydroxy-amide **20** in THF-HMPA was added 0.85 mL (1.35 g, 7.5 mmol) of *iso*-butyl iodide. The resulting mixture was stirred at 25°C for 12 h, then quenched with water. The standard isolation procedure, partitioning between ether-brine and extraction with three portions of methylene chloride, afforded a mixture of alkylation products. Chromatography on silica gel (150 g, ethyl acetate) and bulb-to-bulb distillation afforded 780 mg (61%) of hydroxy-amide **18** as a colorless liquid: IR (neat) 3400, 2950, 2865, 1610, 1435 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.10 (br s, 1, O$\underline{H}$), 4.17 (m, 1, N-C$\underline{H}$), 3.78-3.33 (m, 4, N, O-C$\underline{H}_2$), 2.44-1.39 (m,

10, $C\underline{H}_2$), 0.91 (d, J = 6.5 Hz, 6, $C\underline{H}_3$).

Anal. calcd. for $C_{11}H_{21}NO_2$: C, 66.30; H, 10.62. Found: C, 66.07; H, 10.54.

(2S)-1-[(2S)-2-Hydroxymethylpyrrolid-1-yl]-2,4-dimethylpentanoic Acid (46, Table 7, Entry 3). To a cooled (-100°C) solution of lithium enolate derived from 780 mg (3.92 mmol) of hydroxy-amide 18 in THF-HMPA was added 0.3 mL (0.68 g, 4.8 mmol) of methyl iodide. The resulting mixture was slowly warmed to -40°C over 10 h, then quenched with water. The standard isolation procedure (methylene chloride) afforded after chromatography on silica gel (200 g, ethyl acetate) 767 mg (92%) amide 46: IR (neat) 3390, 2955, 2930, 2870, 1635 (sh), 1612, 1460, 1432 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.17 (br s, 1, O$\underline{H}$), 4.19 (m, 1, N-C$\underline{H}$), 3.72-3.29 (m, 4, N, O-$C\underline{H}_2$), 2.63 [m, 1, C(O)-C$\underline{H}$], 2.17-1.11 (m, 7, $C\underline{H}_2$, C$\underline{H}$), 1.11 [d, J = 6.5 Hz, (R)C(O)-CH-$C\underline{H}_3$], 1.08 [d, J = 6.5 Hz, 3, (S)C(O)-CH-$C\underline{H}_3$], 0.88 (d, J = 5.5 Hz, 6, $C\underline{H}_3$-CH-$C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 178.0 ($\underline{C}$=O), 66.9 ($\underline{C}H_2$-OH), 60.9 (N-$\underline{C}$H), 47.4 (N-$\underline{C}H_2$), 43.4 [C(O)-CH-$\underline{C}H_2$], 36.0 [C(O)-$\underline{C}$H], 28.2 ($\underline{C}H_2$), 25.8 (CH_3-$\underline{C}$H-CH_3), 24.4 ($\underline{C}H_2$), 22.9 ($\underline{C}H_3$-CH-CH_3), 22.6 (CH_3-CH-$\underline{C}H_3$), 17.8 [(R)C(O)-$\underline{C}$HCH_3, minor], 17.1 [(S)C(O)CH$\underline{C}H_3$, major]. VPC analysis (OTMS derivative, 22 m methyl silicone, 150°C) showed two peaks at 11.98 (2S, 90.4%) and 12.25 min (2R, 9.6%).

Anal. calcd. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87. Found: C, 67.35; H, 10.79.

Silylation of Amide Enolates. Enolization With sec-Butyllithium. To a cooled solution (-78°C) of 3.2 mL (3.0 mmol) of sec-butyllithium in 10 mL of THF was added 0.44 mL (0.43 g, 3.3 mmol) of diethylpropionamide. The resulting solution was stirred at -78°C for 10 min followed by addition of 0.52 mL of diisopropylamide and 3.1 mL (3.1 mmol) of a 1.0 M solution of tert-butyldimethylsilylchloride in THF. The mixture was warmed to 25°C and stirred for 1 h. The reaction mixture was concentrated in vacuo with protection from moisture, then filtered to afford a mixture of silyl enol ether and C-silylated amide as a pale yellow liquid: 90 MHz ^{1}H NMR (CCl_4) δ 3.52 (q, J = 7 Hz, C=C$\underline{H}$), 3.47-3.0 (m, C-silyl and starting amide), 2.72 (q, J = 7 Hz, N-C$\underline{H}_2$), 2.19 (q, J = 7.5 Hz, starting amide), 1.4 (d, J = 7 Hz, C=CHC$\underline{H}_3$), 1.20-0.67 (m).

Enolization With LDA. To a cooled solution (0°C) of LDA in 5 mL of THF was added 0.22 mL (0.21 g, 1.6 mmol) of diethylpropionamide. The solution was stirred at 0°C for 10 min followed by addition of 0.27 mL of HMPA and 1.6 mL (1.6 mmol) of a 1.0 M solution of tert-butyldimethylsilyl chloride in THF. The solution was warmed to 25°C and stirred 1 h. The mixture was con-

centrated *in vacuo* with protection from moisture, then filtered to afford silyl enol ether as a colorless liquid: 90 MHz ^{1}H NMR (CCl_4) δ 3.52 (q, J = 7 Hz, 1, C=C$\underline{H}$), 2.72 (q, J = 7 Hz, 4, N-C$\underline{H}_2$), 2.56 (d, J = 9 Hz, HMPA), 1.40 (d, J = 7 Hz, 3, CHC$\underline{H}_3$), 0.87 (s, 9, *t*-Bu), 0.87 (t, J = 7 Hz, 6, NCH$_2$C$\underline{H}_3$), -0.09 (s, 3, SiC$\underline{H}_3$).

General Procedure for the Observation of Lithium Enolates by ^{13}C NMR. To a dried, argon flushed 10 mm NMR tube was added 1.0 equiv of the appropriate base in THF. To the solution was added 1.0 equiv of 3-^{13}C-pyrrolid-1-yl propionamide. ^{13}C NMR was recorded at 35°C using 10% C_6D_6 as an internal lock.

1-[2-(Dihexylboroxymethyl)-pyrrolid-1-yl]-propionic Acid (22). To a solution of 1.80 g (11.5 mmol) of hydroxyamide 15 in 15 mL of benzene was added 3.1 mL (2.6 g, 12.0 mmol) of dihexylchloroborane.[41] The resulting mixture was stirred at 25°C for 1.5 h with evolution of HCl noted. The mixture was concentrated under aspirator vacuum with protection from moisture. The residue was diluted with 5 mL of benzene and concentrated to give amide 22 as a pale yellow liquid: ^{13}C NMR ($CDCl_3$) δ 173 (C=O), 65 (O-$\underline{C}H_2$), 58 (N-$\underline{C}H$), 48 (N-C$\underline{H}_2$), 32 (sh), 32, 27, 24, 23, 20, 14 (CH_3), 9 [C(O)CH$_2$$\underline{C}H_3$]. NOTE: This procedure is not recommended due to the difficulty in removing traces of HCl.

1-[2-(Dicyclohexylboroxymethyl)-pyrrolid-1-yl]-propionic Acid (24). To a solution of 856 mg (4.8 mmol) of dicyclohexylborane in 20 mL of THF was added 747 mg (4.8 mmol) of hydroxyamide 15. Upon cessation of gas evolution the solution was concentrated to give amide 24 as a colorless liquid: ^{13}C NMR ($CDCl_3$) δ 172.5 (C=O), 64.5 (O-CH_2), 57.5 (N-CH), 47.5 (N-CH_2), 28.2, 27.5, 27.1, 27.0, 24.3 (CH_2-CH_3), 8.9 (CH_2CH_3).

1-[2-(Dicyclopentylboroxymethyl)-pyrrolid-1-yl]-propionic Acid (25). To a solution of 429 mg (2.7 mmol) of hydroxyamide 15 in benzene was cautiously added 100 mg (4.2 mmol) of sodium hydride (oil-free). Upon cessation of gas evolution 0.51 mL (0.51 g, 2.8 mmol) of dicyclopentylchloroborane[41] was added to the slurry. Additional gas evolution was noted. The resulting mixture was stirred for several hours with eventual solution of the slurry and formation of a new white precipitate. The mixture was filtered under an inert atmosphere using Schlenk apparatus. The clear filtrate was concentrated to give 25 as a clear liquid: ^{1}H NMR ($CDCl_3$) δ 4.8-4.2 (m, 1, N-CH), 4.2-3.5 (m, 4, N, O-CH_2), 2.73 (q, J = 7.5 Hz, 2, CH_2CH_3), 2.3-1.9 (m, 4, CH_2), 1.9-1.0 (m, 18), 1.31 (t, J = 7.5 Hz, 3, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 176 (C=O), 64 (O-CH_2), 61 (N-CH), 49 (N-CH_2), 28, 28 (sh), 27, 24 (CH_2-CH_3), 10 (CH_3).

General Procedures for the Diastereoselective Alkylation of Borate Derivatives. Preparation of Potassium Hexamethyldisilylamide. A slurry of 1.0 equiv of potassium hydride in mineral oil was washed with four portions of pentane to remove the oil. To the residue was added a sufficient volume of THF to afford a 0.5-1.0 M solution upon addiiton of 1.0 equiv of hexamethyldisilylazide. The resulting mixture was stirred until gas evolution ceases then permitted to stand undisturbed for 8-10 h. The supernatant was used as a standard solution.

Ate-Complex Alkylation Conditons. To a stirred solution of 1.1 equiv of the appropriate base in THF (0.1-0.5 M) was added 1.0 equiv of amide derivative. The resulting solution was stirred for 10-30 min followed by addition of HMPA. The mixture was cooled to the appropriate alkylation temperature and 1.1-1.5 equiv of ethyl iodide was added dropwise. The reaction mixture was stirred 6-12 h.

Oxidative Isolation Procedure. The resulting reaction mixture was quenched by addition of water followed by 10 equiv each of 10% aqueous NaOH and 30% H_2O_2. The mixture was stirred until gas evolution ceases (1-2 h) then partitioned between methylene chloride and brine. The aqueous layer was extracted

with 2-3 portions of methylene chloride. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Filtration through silica afforded the alkylation product which was analyzed by gas chromatography.

1-[2(S)-Methoxymethylpyrrolid-1-yl]-propionic Acid (30).[5a] To a solution (0°C) of 3.573 g (22.8 mmol) of hydroxyamide 15 in 50 mL of THF was cautiously added 1.0 g (4.2 mmol) of sodium hydride (oil-free). Upon cessation of gas evolution the resulting slurry was warmed to 25°C. Addition of 2.2 mL (33.4 mmol) of methyl iodide results in first partial solution then formation of a new white precipitate. The resulting mixture was stirred for 15 h then carefully quenched by addition to water. The mixture was partitioned between ether-brine and the aqueous phase extracted with two portions of ether. The combined organics were dried ($MgSO_4$) and concentrated. Chromatography on silica gel (ethyl acetate) and bulb-to-bulb distillation affords 2.869 g (74%) of methyl ether 30 as a colorless liquid: IR ($CHCl_3$) 3000, 2990, 2940, 2875, 1627, 1457, 1444 (sh), 1428, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.37-3.93 (m, 1, N-C$\underline{H}$), 3.67-3.17 (m, 4, N, O-C$\underline{H}_2$), 3.32 (s, 3, OC$\underline{H}_3$), 2.23 (q, J = 8 Hz, 2, C$\underline{H}_2$CH$_3$), 2.07-1.77 (m, 4, C$\underline{H}_2$), 1.12 (t, J =

8 Hz, 3, $CH_2\underline{CH_3}$); ^{13}C NMR ($CDCl_3$) δ 172.8 ($\underline{C}$=O), 72.5 ($O\underline{CH_3}$), 60.0 ($O\underline{CH_2}$), 56.4 (N-$\underline{C}$H), 47.2 (N-$\underline{CH_2}$), 28.1 ($\underline{CH_2}$), 27.5 ($\underline{CH_2}$), 24.2 ($\underline{CH_2}CH_3$), 8.9 ($CH_2\underline{CH_3}$).

1-[(2S)-Methoxyethoxymethoxymethylpyrrolid-1-yl]-propionic Acid (32). To a cooled (0°C) slurry of 1.25 g (52.1 mmol) of oil-free sodium hydride in 60 mL of THF was slowly added a THF solution of 4.89 g (31.1 mmol) of hydroxy-amide 15. The resulting mixture was stirred until gas evolution ceases, then warmed to 25°C and 5.3 mL (5.7 g, 46.4 mmol) of MEM-chloride was added. The reaction mixture was stirred at 25°C for 10 h then carefully quenched with water. The mixture was partitioned between methylene chloride-brine and the aqueous phase extracted with two portions of methylene chloride. The combined organics were dried (Na_2SO_4) and concentrated (in vacuo). Bulb-to-bulb distillation (bp 110°, < 0.001 mm) afforded 7.14 g (94%) MEM ether 32 as a colorless liquid: IR (CCl_4) 2982, 2945, 2882, 2820, 1648, 1460, 1448, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.64 (s, 2, O-$\underline{CH_2}$-O), 4.37-3.88 (m, 1, N-$\underline{C}$H), 3.78-3.28 (m, 8, N, O-$\underline{CH_2}$), 3.36 (s, 3, $O\underline{CH_3}$), 2.26 (overlapping q, J_1 = 7 Hz, 2, $\underline{CH_2}$-CH_3), 2.06-1.78 (m, 4, $\underline{CH_2}$), 1.11 (overlapping t, J = 7 Hz, 3, CH_2-$\underline{CH_3}$); $[\alpha]_D$ = -59.9° (c 9.1, CH_2Cl_2).

Anal. calcd. for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45. Found: C, 58.85; H, 9.46.

1-[2(S)-*tert*-Butyldimethylsilyloxymethylpyrrolid-1-yl]-propionic Acid (33). To a solution of 4.8 g (30.6 mmol) of hydroxy-amide 15 and 5.3 g (77.8 mmol) of immidazole in 40 mL of DMF was added 5.8 g (38.4 mmol) of *tert*-butyldimethylsilyl chloride. The resulting mixture was stirred at 25°C for 10 h, then partitioned between hexane-brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel (hexane-ethyl acetate) and bulb-to-bulb distillation (100°C, <0.001 mm) afforded 8.06 g (97%) of silyl ether 33 as a colorless liquid: IR (neat) 2962, 2942, 2865, 1650, 1462, 1422, 1257, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14-3.72 (m, 1, N-C*H*), 3.58 (overlapping d, J_1 = 5 Hz, J_2 = 6 Hz, 2, C*H*$_2$OSi), 3.51-3.18 (m, 2, N-C*H*$_2$), 2.17 (overlapping q, J_1 = 7 Hz, 2, CH_3C*H*$_2$), 2.04-1.61 (m, 4, C*H*$_2$), 1.01 (t, J = 7 Hz, 3, C*H*$_3$), 0.78 (s, 9, *t*-C_4*H*$_9$), -0.04 (overlapping s, 6, SiC*H*$_3$); $[\alpha]_D$ = -63.4° (*c* 9.26, CH_2Cl_2).

Anal. calcd. for $C_{14}H_{29}NO_2Si$: C, 61.94; H, 10.77. Found: C, 61.78; H, 10.85.

1-[2-Dimethylhydroxymethylpyrrolid-1-yl]-propionic Acid (36). To a solution (25°C) of 1.21 g (4.6 mmol) of N-propionylproline benzyl ester[60] in 50 mL of THF was added 3.6 mL (10 mmol) of a 2.8 *M* solution of methyl magnesium bromide in ether. The resulting

mixture was stirred for 2 h then quenched with saturated aqueous ammonium chloride. The mixture was partitioned between methylene chloride and water. The organics were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel (HPLC, 50% ethyl acetate/hexane) afforded 0.36 g (42%) of amide **36** as a pale yellow oil: IR (neat) 3300, 2980, 2950, 2885, 1620, 1465, 1432 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.42 (br s, 1, O<u>H</u>), 4.09 (t, J = 8 Hz, 1, N-C<u>H</u>), 3.8-3.17 (m, 2, N-C<u>H</u>$_2$), 2.39 (q, J = 7.5 Hz, 2, C<u>H</u>$_2$CH$_3$), 2.23-1.4 (m, 4, C<u>H</u>$_2$), 1.17 (s, 3, CH_3), 1.14 (t, J = 7.5 Hz, 3, CH_2C<u>H</u>$_3$), 1.03 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 175.4 (s, <u>C</u>=O), 73.4 (s, <u>C</u>-OH), 68.0 (d, N-<u>C</u>H), 48.8 (t, N-C<u>H</u>$_2$), 28.7 (t, CH_2), 27.9 (t, CH_2), 24.5 (t, <u>C</u>H$_2$CH$_3$), 23.2 [q, C(<u>C</u>H$_3$)$_2$], 9.2 (q, CH_2<u>C</u>H$_3$).

1-[2-Dimethyl-(*tert*-butyldimethylsilyloxy)-methylpyrrolid-1-yl]-propionic Acid (**37**). To a solution (25°C) of 404 mg (2.2 mmol) of hydroxyamide **36**, 450 mg (6.6 mmol) of imidazole, 1 mg of dimethylaminopyridine in 2 mL of DMF was added 420 mg (28 mmol) of *tert*-butyldimethylsilyl chloride. The resulting mixture was stirred for 24 h. The reaction mixture was portioned between hexane-water and the aqueous layer extracted with an additional portion of brine. The combined organics were dried ($MgSO_4$) and concentrated

to afford silyl ether 37 as a colorless liquid: IR (neat) 2968, 2945, 2895, 2870, 1658, 1412, 1255, 1155, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.2-4.03 (m, 1, N-C<u>H</u>), 3.7-3.13 (m, 2, N-C<u>H</u>$_2$), 2.33 (q, J = 7 Hz, 2, C<u>H</u>$_2$CH$_3$), 1.13 [s, 6, C(CH$_3$)$_2$], 1.04 (t, J = 7 Hz, 3, CH$_2$C<u>H</u>$_3$), 0.77 (s, 9, <u>t</u>-Bu), 0.01 (s, 3, SiC<u>H</u>$_3$), -0.01 (s, 3, SiC<u>H</u>$_3$).

2-Hydroxymethyl-5-methylpyrrolidine.[23] To a stirred solution of 2.43 g (18.9 mmol) of 5-methylproline[46] and 2.5 mL of boron trifluoride etherate in 10 mL of THF was added 22 mL (22 mmol) of a 1.0 <u>M</u> solution of borane in THF dropwise over 1 h. Following complete addition the reaction mixture was heated to reflux for 2 h. The resulting solution was cooled and carefully quenched with 1 mL of 50% aqueous THF then 10 mL of 6 <u>N</u> NaOH. The resulting vigorously stirred mixture was heated to reflux for 3 h then cooled and stirred for an additional 8 h. The organic layer was separated and the aqueous layer extracted with three portions of ether. The combined organics were dried (K_2CO_3) and concentrated to afford 1.58 g (73%) of 2-hydroxymethyl-5-methylpyrrolidine as a clear liquid: IR (neat) 3300, 2975, 2890, 1462, 1387, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6-2.8 (overlapping m, 6), 1.9-1.1 (m, 4), 1.04 (d, J = 6 Hz, 3, C<u>H</u>$_3$).

1-[2-Hydroxymethyl-5-methylpyrrolid-1-yl]-propionic Acid (38, 40). Following the general procedure acylation of 3.0 g (26 mmol) of 2-hydroxymethyl-5-methylpyrrolidine with 3.7 mL (3.8 g, 29 mmol) of propionic anhydride affords a mixture of *cis* and *trans*-amides 38 and 40. Chromatography on silica gel (ethyl acetate) gave pure amide 38 as a colorless liquid: IR (neat) 3400, 2980, 2950, 2885, 1620, 1470, 1460, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.66-5.42 (br d, 1, O$\underline{H}$), 4.29-3.82 (m, 2, N-C$\underline{H}$), 3.70 (br d of d, 2, O-C$\underline{H}_2$), 2.33 [q, J = 8 Hz, 2, C(O)C$\underline{H}_2$), 2.16-1.39 (m, 4, C$\underline{H}_2$), 1.19 (d, J = 8 Hz, 3, CHC$\underline{H}_3$), 1.15 (t, J = 8 Hz, 3, $CH_2C\underline{H}_3$).

Anal. calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.01. Found: C, 63.05; H, 10.00.

1-[2-(*tert*-Butyldimethylsilyoxymethyl-5-methylpyrrolid-1-yl]-propionic Acid (39, 41). To a solution (25°C) of 0.60 g (3.5 mmol) of hydroxyamides 38 and 40 in 5 mL of DMF was added 0.95 g (14 mmol) of imidazole and 1.1 g (7.2 mmol) of *tert*-butyldimethylsilyl chloride. The resulting solution was stirred for 13 h then portioned between hexane-water. The aqueous layer was extracted with an additional portion of hexane. The combined organic layers were dried and concentrated to afford 0.80 g (80%) of a

mixture of **39** and **41** as a colorless liquid: IR (neat) 2965, 2945, 2905, 2895, 2870, 1650, 1415, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.16-3.18 (m, 4, N, O-C<u>H</u>), 2.22 (overlapping q, 2, $C\underline{H}_2CH_3$), 2.06-1.29 (m, 4, $C\underline{H}_2$), 1.07 (d, J = 8 Hz, 3, CH-$C\underline{H}_3$), 1.02 (overlapping t, 3, $CH_2C\underline{H}_3$), 0.78 (s, 9, <u>t</u>-Bu), -0.04 (s, 6, $SiC\underline{H}_3$). VPC analysis (25 m Carbowax 20M, 180°C) showed two peaks at 3.09 (**41**, 11.4%) and 3.28 min (**39**, 88.6%).

V. References and Notes

(1) (a) ApSimon, J. W.; Seguin, R. P. Tetrahedron 1979, 35, 2797-2842. (b) Scott, J. W.; Valentine, Jr., D. Science 1974, 184, 943-951. (c) Kagan, H. B.; Fiaud, J. C. Topics in Stereochem. 1978, 10, 175-

(2) For recent reviews see: (a) Westley, J. W. Adv. Appl. Microbiol. 1977, 22, 177-223. (b) Westley, J. W. "Polyether Antibiotics: Carboxylic Acid Ionophores"; in press. (c) Wierenga, W. "Total Synthesis of Ionophores"; in press. (c) Izatt, R. M.; Christensen, J. J. "Progress in Macrocyclic Chemistry, Vol. 1"; Wiley: New York, 1979; p. 79. (e) McGlocklin, S.; Eisenberg, M. Annu. Rev. Bioeng. 1975, 4, 335-366.

(3) For alkylation approaches to chiral aldehydes see: (a) Meyers, A. I.; Brich, Z.; Erickson, G. W. J. Chem. Soc., Chem. Commun. 1979, 566-567. (b) Meyers, A. I.; Brich, Z. Ibid 1979, 567-568. (c) Meyers, A. I.; Poindexter, G. S.; Brich, Z. J. Org. Chem. 1978, 43, 892-898. (d) Enders, D.; Eichenauer, H. Chem. Ber. 1979, 112, 2933-2960. (e) Enders, D.; Eichenauer, H. Tetrahedron Lett. 1977, 191-194. (f) Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. J. Am. Chem. Soc. 1979, 101, 5654-5659. (g) Fraser, R. R.; Akiyama,

F.; Banville, J. Tetrahedron Lett. 1979, 3929-3932.

(4) For alkylation approaches to chiral ketones see: (a) Enders, D.; Eichenauer, H. Angew. Chem. Int. Ed. Engl. 1979, 18, 397-399. (b) Enders, D.; Eichenauer, H. Ibid 1976, 15, 549-551. (c) See also Ref. 3d,g. (d) Hashimoto, S. I.; Koga, K. Chem. Pharm. Bull. 1979, 27, 2760-2766. (e) Hashimoto, S. I.; Koga, K. Tetrahedron Lett. 1978, 573-576. (f) Saigo, K.; Koda, H.; Nohira, H. Bull. Chem. Soc. Jap. 1979, 52, 3119-3120. (g) Worster, P. M.; McArthur, C. R.; Leznoff, C. C. Angew. Chem. Int. Ed. Engl. 1979, 18, 221-222. (h) Meyers, A. I.; Williams, D. R. J. Org. Chem. 1978, 43, 3245-3247. (i) Meyers, A. I.; Williams, D. R.; Druelinger, M. J. Am. Chem. Soc. 1976, 98, 3032-3033. (j) Whitesell, J. K.; Whitesell, M. A. J. Org. Chem. 1977, 42, 377-378.

(5) For alkylation approaches to chiral carboxylic acids see: (a) Sonnet, P. E.; Heath, R. R. J. Org. Chem. 1980, 45, 3139-3141. (b) Ade, E.; Helmchen, G.; Heilgenmann, G. Tetrahedron Lett. 1980, 21, 1137-1140. (c) Larcheveque, M.; Ignatova, E.; Cuvigny, T. J. Organomet. Chem. 1979, 177, 5-15. (d) Larcheveque, M.; Ignatuva, E.; Cuvigny, T. Tetrahedron Lett. 1978, 3961-3964. (e) Meyers, A. I.

Pure & Appl. Chem. 1979, 51, 1255-1268. (f) Meyers, A. I.; Mihelich, E. D. Angew. Chem. Int. Ed. Engl. 1976, 15, 270-281. (g) Meyers, A. I.; Mazzu, A.; Whitten, C. E. Heterocycles 1977, 6, 971-977. (h) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. J. Am. Chem. Soc. 1976, 98, 567-576. (i) Meyers, A. I.; Mihelich, E. D. J. Org. Chem. 1975, 40, 1186-1187. (j) Meyers, A. I.; Knaus, G.; Kendall, P. M. Tetrahedron Lett. 1974, 3495-3498. (k) Hansen, J. F.; Cooper, C. S. J. Org. Chem. 1976, 41, 3219-3220. (l) Kaneko, T.; Turner, D. L.; Newcomb, M.; Bergbreiter, D. E. Tetrahedron Lett. 1979, 103-106. (m) Fräter, G. Helv. Chim. Acta 1979, 62, 2825-2828, 2829-2832. (n) Kolb, M.; Barth, J. Tetrahedron Lett. 1979, 2-99-3002. (o) Yamada, S.-I.; Oguri, T.; Shioiri, T. J. Chem. Soc., Chem. Commun. 1976, 136-137. (p) Nakatsuka, S.; Miyazaki, H.; Guto, T. "Abstracts of Papers", Nippon Nogei Kagakukai Annual Meeting, Tokyo, April, 1979, p. 328. (q) Schöllkopf, U.; Hausberg, H. H.; Hoppe, I.; Segal, M.; Reiter, U. Ibid 1978, 17, 117-119.

(6) (a) Evans, D. A.; Takacs, J. M. Tetrahedron Lett. 1980, 21, 4233-4236. (b) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. E.; Mathre, D. J.; Bartroli, J. Pure & Appl. Chem. 1980, 52, in press.

(7) (a) Ireland, R. E.; Wilcox, C. S. Tetrahedron Lett. 1977, 2839-2842. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. J. Am. Chem. Soc. 1976, 98, 2868-2877.

(8) (a) Nelson, J. V. Ph.D. Dissertation, California Institute of Technology, 1981. (b) Evans, D. A.; Vogel, E.; Nelson, J. V. J. Am. Chem. Soc. 1979, 101, 6120-6123. (c) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. J. Org. Chem. 1980, 45, 1066-1081.

(9) (a) Meyers, A. I.; Snyder, E. S.; Ackerman, J. J. H. J. Am. Chem. Soc. 1978, 100, 8186-8189. (b) Hoobler, M. A.; Bergbreiter, D. E.; Newcomb, M. Ibid 1978, 100, 8182-8185. (c) See Ref. 3f.

(10) (a) Evans, D. A.; McGee, L. R. Tetrahedron Lett. 1980, 21, 3975-3978. (b) Yamamoto, Y.; Maruyama, K. Ibid 1980, 21, 4607-4610. (c) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. J. Am. Chem. Soc. 1980, 102, 7109-7110.

(11) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. J. Am. Chem. Soc. 1980, 102, 3959-3960.

(12) The nomenclature for describing enolate geometry can be confusing. In the present work, cis and trans invariably describe the relationship between the carbonyl oxygen (or sulfur) and the α-substituent.

(13) Data in Table 1 taken from sources listed in

References 3f, 8, 9, 11.

(14) Woodbury, R. P.; Rathke, M. W. J. Org. Chem. 1978 43, 881-884.

(15) Ficini, J. Tetrahedron 1976, 32, 1448-1486.

(16) House, H. O.; Kramar, V. J. Org. Chem. 1963, 28, 3362-3379.

(17) Meyers, A. I.; Reider, P. J. J. Am. Chem. Soc. 1979, ___, 2501-2502.

(18) Pirrung, M. C.; Heathcock, C. H. J. Org. Chem. 1980, 45, 1727-1728.

(19) (a) Sucrow, W.; Richter, W.; Chem. Ber. 1971, 104, 3679-3688. (b) Jenkins, P. R.; Gut, R.; Wetter, H.; Eschenmoser, A. Helv. Chim. Acta 1979, 62, 1922-1931.

(20) Bartlett, P. A.; Hahne, W. F. J. Org. Chem. 1979, 44, 882-883.

(21) Tamaru, Y.; Harada, T.; Yoshida, Z.-I. J. Am. Chem. Soc. 1978, 100, 1923-1925.

(22) (a) Schuijl, P. J. W.; Brandsma, L.; Arens, J. F. Rec. Trav. Chim. Pays-Bas 1966, 85, 1263-1265. (b) Gomper, R.; Elser, W. Liebigs Ann. Chem. 1969, 725, 64-72. (c) Tamaru, Y.; Harada, T.; Yoshida, Z.-I. J. Am. Chem. Soc. 1980, 102, 2392-2398. (d) Tamaru, Y.; Harada, T.; Nishi, S.-I.; Mizutani, M.; Hioki, T.; Yoshida, Z.-I. J. Am. Chem. Soc. 1980, 102, 7808-7809.

(23) Lane, C. F. U.S. Patent 3 935 280, 1976.

(24) For application of this concept in total synthesis see (a) Collum, D. B.; McDonald, III, J. H.; Still, W. C. J. Am. Chem. Soc. 1980, 102, 2117-2118, 2118-2120, 2120-2121. (b) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. Ibid 1979, 101, 262-263. (c) Corey, E. J.; Kim, S.; Yoo, S.-E.; Nicolaou, K. C.; Melvin, Jr., L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. Ibid 1978, 100, 4620-4622. (d) Woodward, R. B., erythromycin synthesis presented in part at the 25th National Organic Chemistry Symposium, June, 1977.

(25) (a) Chan, K.-K.; Saucy, G. J. Org. Chem. 1977, 42, 3828-3832. (b) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. Angew. Chem. Int. Ed. Engl. 1979, 63-65. (c) Helmachen, G.; Nill, G. Ibid 1979, 65-66. (d) Pirkle, W. H.; Adams, P. E. J. Org. Chem. 1980, 45, 4111-4117.

(26) Phillips, A. P.; Baltzly, R. J. Am. Chem. Soc. 1947, 69, 200-204.

(27) (a) Venkatasubban, K. S.; Hogg, J. F. Tetrahedron Lett. 1979, 4355-4358. (b) Lee, Y.-N.; Schmir, G. L. J. Am. Chem. Soc. 1979, 101, 3026-3035. (c) Fife, T. H.; Przystas, T. J.; Squillacote, V. L. Ibid 1979, 101, 3017-3026.

(28) Jackman, L. M.; Szeverenyi, N. M. J. Am. Chem. Soc. 1977, 99, 4954-4962.

(29) Young, P. R.; Jencks, W. P.; J. Am. Chem. Soc. 1979, 101, 3288-3294.

(30) (a) Heathcock, C. H.; White, C. T. J. Am. Chem. Soc. 1979, 101, 7076-7077. (b) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; Vanderveer, D. J. Org. Chem. 1980, 45, 3846-3856.

(31) (a) Meyers, A. I.; Kamata, K. J. Org. Chem. 1974, 39, 1603-1604. (b) Meyers, A. I.; Kamata, K.; J. Am. Chem. Soc. 1976, 98, 2290-2294. (c) von Schriltz, D. M.; Hampton, K. G.; Hauser, C. R. J. Org. Chem. 1969, 34, 2509-2511. (d) Kenyon, W. G.; Meyer, R. B.; Hauser, C. R. Ibid 1963, 28, 3108-3112.

(32) Enders, D.; Eichenauer, H.; Pieter, R. Chem. Ber. 1979, 112, 3703-3714.

(33) Rathke, M. W.; Lindert, A. Synth. Commun. 1978, 8, 9-14.

(34) Negishi, E.-I.; Idacavage, M. J. Tetrahedron Lett. 1979, 845-848.

(35) For other possible examples see: (a) Fortunato, J. M.; Ganem, B. J. Org. Chem. 1976, 41, 2194-2200. (b) Pasto, D. J.; Wojtkowski, P. W. Ibid 1971, 36, 1790-1792.

(36) Idacavage, M. J.; Negishi, E.-I.; Brown, C. A.

J. Organomet. Chem. 1980, 186, C55-C57.

(37) (a) Tufariello, J. J.; Lee, L. T. C.; Wojkowski, P. J. Am. Chem. Soc. 1967, 89, 6804-6805. (b) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. Tetrahedron Lett. 1979, 1665-1668, and references therein. (c) See also: Kramer, G. W.; Brown, H. C. J. Organomet. Chem. 1977, 132, 9-27.

(38) In carrying out the exchange cycle, lithium enolate to boron enolate to lithium enolate, the enolate stereochemistry is scrambled as judged by analysis of the derived silyl enol ethers. Evans, D. A.; Nelson, J. V. Personal communication, 1979.

(39) An in situ preparation of borate 25 followed by addition of base, however, shows quite different reactivity (Table 8, Entry 29).

(40) 9-Borabicyclo[3.3.1]nonane.

(41) (a) Brown, H. C.; Ravindran, N. J. Am. Chem. Soc. 1973, 95, 2396-2397. (b) Brown, H. C.; Ravindran, N. Ibid 1972, 94, 2112-2113.

(42) Brown, H. C.; Klender, G. J. Inorg. Chem. 1962, 1, 204-214.

(43) We wish to thank Dr. P. A. Sonnet for communication of his independent observations in this area prior to publication. See Ref. 5a.

(44) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser,

A.; Hobi, R.; Kratky, C. Helv. Chim. Acta 1978, 61, 3108-3135.

(45) Ahlbrecht, H.; Becher, G.; Blecher, J.; Kalinowski, H.-O.; Raab, W.; Mannschreck, A. Tetrahedron Lett. 1979, 2265-2268.

(46) Overberger, C. G.; David, K.-H.; Moore, J. A. Macromolecules 1965, 5, 368-372.

(47) Poindexter, G. S.; Meyers, A. I. Tetrahedron Lett. 1977, 3527-3528. See also Ref. 23.

(48) Note that since we analyze at the diastereomer stage, we need only look at the relative asymmetric induction to judge the overall efficiency. Hence, racemic starting materials can be used.

(49) Prepared compounds are compared against the highest available literature rotation for chiral material.

(50) Watson, S. L.; Eastham, J. F. J. Organomet. Chem. 1967, 9, 165-168.

(51) Kjaer, A.; Hansen, S. E. Acta Chem. Scand. 1957, 11, 898-900.

(52) Levene, P. A.; Marker, R. E. J. Biol. Chem. 1932, 98, 1-7.

(53) Levene, P. A.; Bass, L. W. J. Biol. Chem. 1926, 70, 211-217.

(54) (a) We wish to thank Drs. M. Crimmins and U. Strauss for preparation of these iodides. (b) Taber, T. R.

Ph.D. Dissertation, California Institute of Technology, 1981, and references therein.

(55) The structure was proved by conversion to Prelog-Djerassi lactone. Dr. U. Strauss, unpublished results.

(56) Prepared from the chiral acid (Table 2, Entry H) by LAH reduction, mesylation and displacement with sodium iodide.

(57) Performed on distilled material.

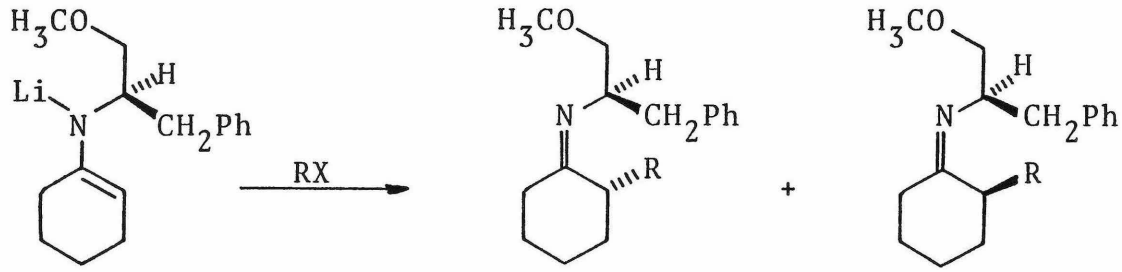
(58) Fray, G. I.; Polgar, N. J. Chem. Soc. 1956, 2036-2041.

(59) Prepared by the reaction of proline benzyl ester with propionic anhydride.

VI. APPENDIX I

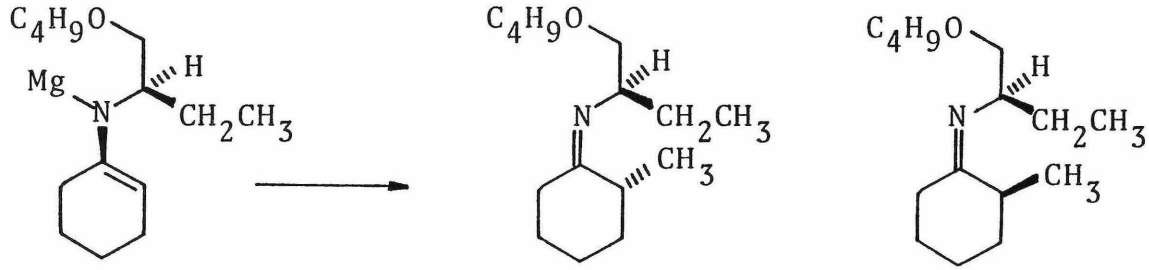
Tabulation of Diastereoselective Alkylations of Chiral Enolates[1]

I. CYCLIC KETONE DERIVATIVES



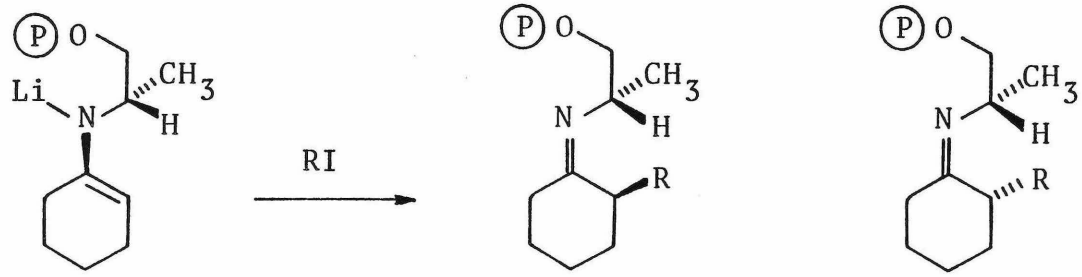
Ref. 2

RX	Alkylation Temp.	Ketones		Yield
$(CH_3)_2SO$	-78	91	9	72
CH_3CH_2I	-78	major	--	56
$CH_3CH_2CH_2I$	-78	>97.5	2.5	50
$CH_2{=}CHCH_2Br$	-98	>95	5	80
$PhCH_2Br$	-98	major	--	56



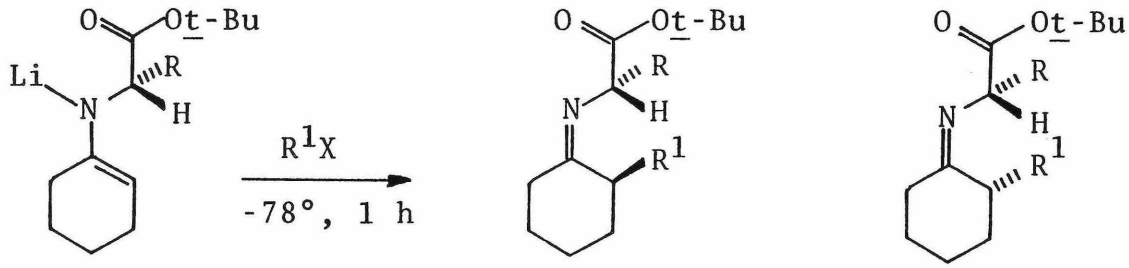
3

Alkylation Temp.	Ketones	
-78 → 0°	90.5	9.5
-100 → 0°	92.5	7.5
68°	60	40



Ref. 4

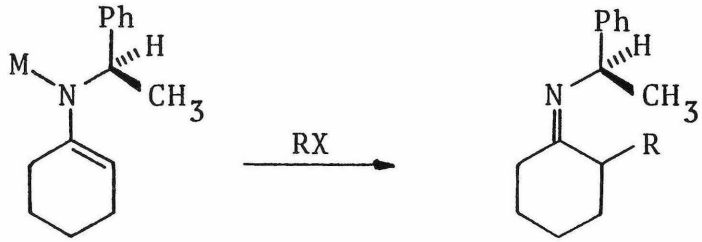
	Ketones		Yield
R = CH_3	97.5	2.5	80
$CH_3CH_2CH_2$	80	20	80



Ref. 5

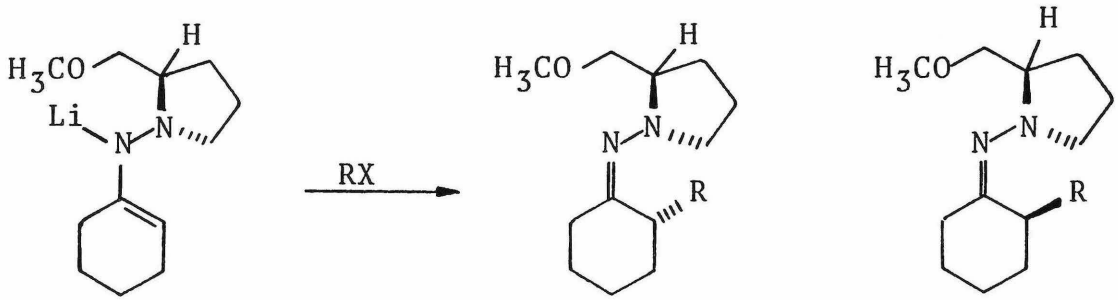
R	R^1X	Ketones		Yield
i-C_3H_7	$(CH_3)_2SO_4$	92	8	59
i-C_3H_7	$CH_2{=}CHCH_2Br$	86.5	13.5	71
t-C_4H_9[a]	$(CH_3)_2SO_4$	99	1	65
t-C_4H_9	CH_3I	98.5	1.5	57
t-C_4H_9	$CH_3CH_2CH_2I$	98.5	1.5	70
t-C_4H_9	$CH_2{=}CHCH_2Br$	92	8	75

[a]Optical yield based on 90.5% ee in starting material.



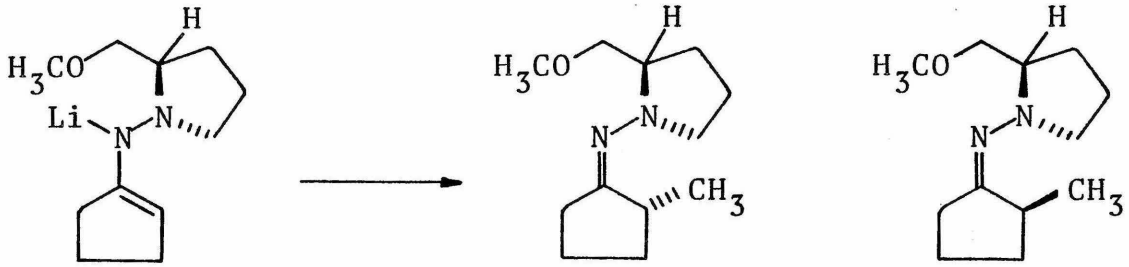
Ref. 6

M	RX	Diasteriomer Ratio
Mg	CH_3I	76:24
Li	CH_3I	66:34
Li	$(CH_3)_2SO_4$	57:43
Li	CH_3CH_2I	58:42
Li	CH_3CH_2Br	68:32

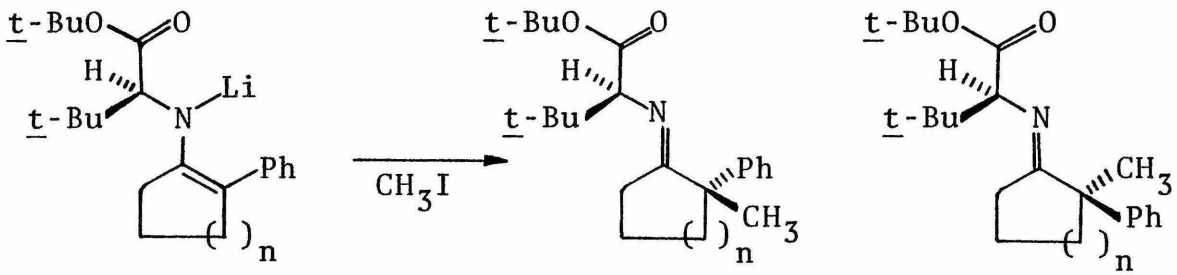


Ref. 7

RX	Ketones		Yield
$(CH_3)_2SO_4$	92.5	7.5	80
CH_3I	82	18	82
CH_3CH_2I	>75	25	80
$CH_3CH_2CH_2I$	93.5	6.5	81
$CH_2=CHCH_2Br$	91	9	67



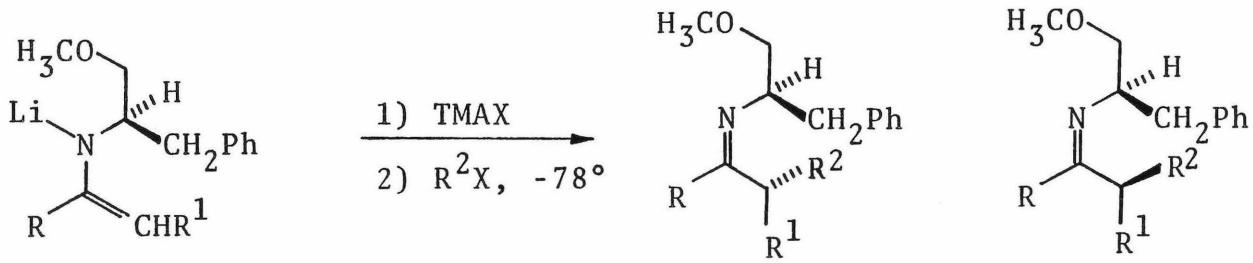
Ketones		Yield	Ref.
72.5	27.5	82	7



	Ketones		Yield	
n = 1[a]	97	3	62	5
n = 2	98	2	40	

a = optical purity of starting material 85.1%.

II. ACYCLIC KETONE DERIVATIVES

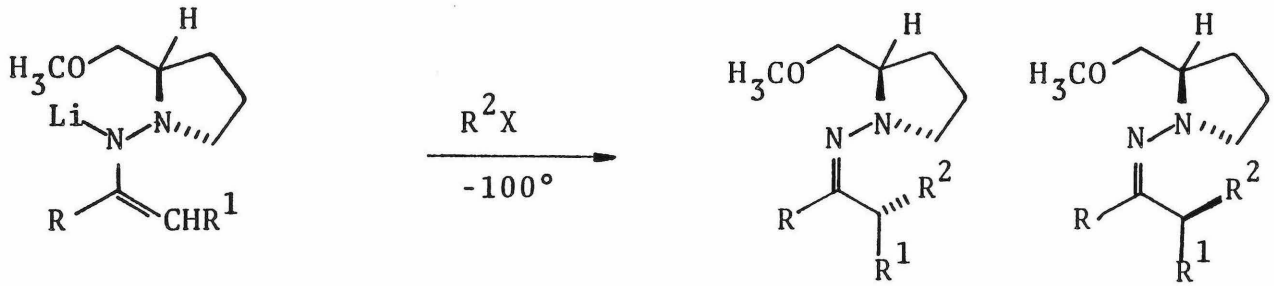


Ref.

8

R	R^1	R^2X	TMAX°	Ketones		Yield
CH_3CH_2	CH_3	CH_3CH_2I	-20	51.5	48.5	--
CH_3CH_2	CH_3	CH_3CH_2I	-20	84.5[a]	15.5	--
CH_3CH_2	CH_3	CH_3CH_2I	65	88	12	48
$CH_3CH_2CH_2$	CH_3CH_2	CH_3I	-20	71.5	28.5	--
$CH_3CH_2CH_2$	CH_3CH_2	CH_3I	65	99	1	84
$CH_3CH_2CH_2CH_2$	$CH_3CH_2CH_2$	CH_3I	-20	72.5	27.5	--
$CH_3CH_2CH_2CH_2$	$CH_3CH_2CH_2$	CH_3I	65	94	6	75
Ph	CH_3	CH_3CH_2I	-20	72	28	--
Ph	CH_3	CH_3CH_2I	65	76.5	23.5	80
Ph	CH_3CH_2	CH_3I	65	67.5	32.5	77
Ph	Ph	CH_3I	65	60	40	88
$PhCH_2$	Ph	CH_3I	-20	62.5	37.5	--
$PhCH_2$	Ph	CH_3I	65	70.5	29.5	90

[a]Anion made with LTMP; all others use LDA.

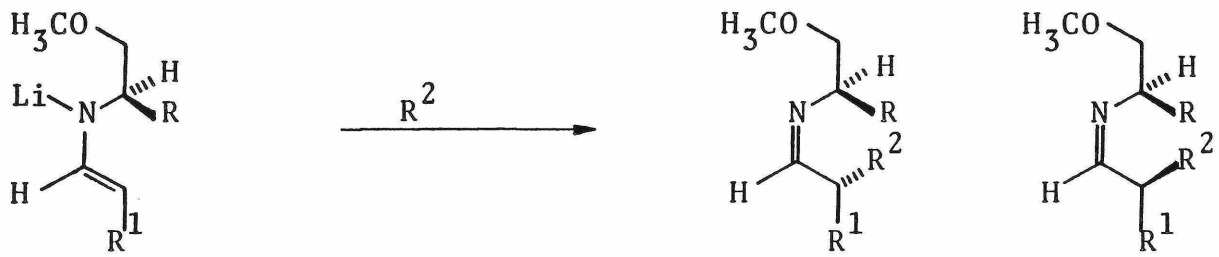


Ref.

7

R	R^1	R^2X	Solvent	Ketones		Yield
CH_3CH_2	CH_3	CH_3CH_2I	THF	80	20	76
CH_3CH_2	CH_3	CH_3CH_2I	Et_2O	96	4	61
CH_3CH_2	CH_3	$CH_3CH_2CH_2I$	Et_2O	99.8	0.2	60
$CH_3CH_2CH_2$	CH_3CH_2	CH_3I	Et_2O	>99	1	55
$CH_3CH_2CH_2CH_2$	$CH_3CH_2CH_2$	CH_3I	Et_2O	>99	1	54
$PhCH_2$	Ph	CH_3I	THF	35	65	81

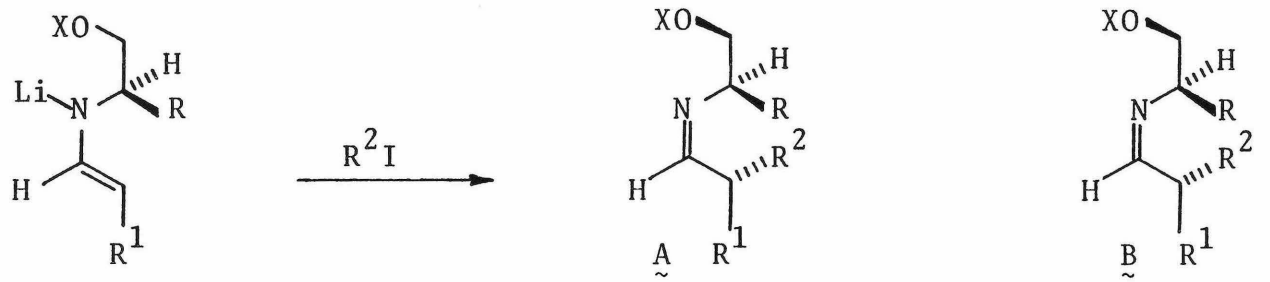
III. ALDEHYDE DERIVATIVES



Ref.

9

Amine	R	R^1	R^2	Aldehydes		Yield
S	iC_3H_7	CH_3	hexyl	63	37	76
S	iC_3H_7	hexyl	CH_3	60.5	39.5	67
S	iC_4H_9	CH_3	hexyl	64.5	29	62
S	iC_4H_9	hexyl	CH_3	67	33	72
R	$(C_6H_{11})CH_2$	CH_3	hexyl	58.5	41.5	34
R	$(C_6H_{11})CH_2$	hexyl	CH_3	62.5	37.5	62
S	$PhCH_2$	CH_3	hexyl	71	29	36
S	$PhCH_2$	hexyl	CH_3	73.5	26.5	46
R	Ph	CH_3	hexyl	68.5	31.5	67
R	Ph	hexyl	CH_3	66.5	33.5	59

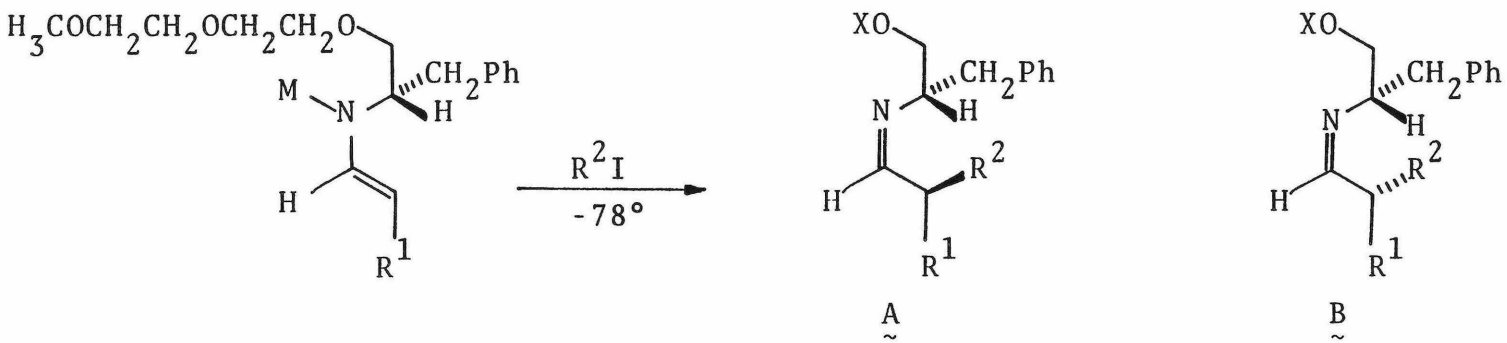


Ref. 9

Amine	R	X	$R^1=CH_3$; R^2=hexyl A	B	Yield	R^1=hexyl; $R^2=CH_3$ A	B	Yield
S	iC_4H_9	OCH_3	64.5	35.5	62	67	33	72
S	iC_4H_9	$OCH_2CH_2OCH_3$	71	29	74	68.5	31.5	73
S	iC_4H_9	$OCH_2CH_2CH_2OCH_3$	60	40	53	--	--	--
R	Ph	OCH_3	68.5	31.5	67	66.5	33.5	59
R	Ph	$OCH_2CH_2OCH_3$	76	24	70	65.5	34.4	57
S	$PhCH_2$[a]	OCH_3	71	29	36	73.5	26.5	46
S	$PhCH_2$	$OCH_2CH_2OCH_3$	69.5	30.5	70	--	--	--
S	$PhCH_2$	$OCH_2CH_2N(CH_3)_2$	--	--	--	77[b]	23	75
S	$PhCH_2$	$OCH_2CH_2OCH_2CH_2OCH_3$	75.5	24.5	60	74	26	48

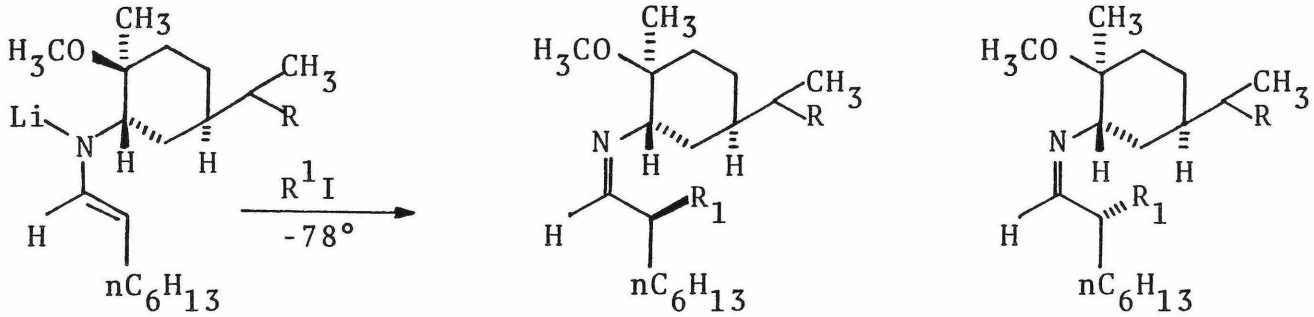
[a]Optical yield estimated from aldehyde which is 75% chemically pure.

[b]Used Li LTMP as base; all others use LDA.



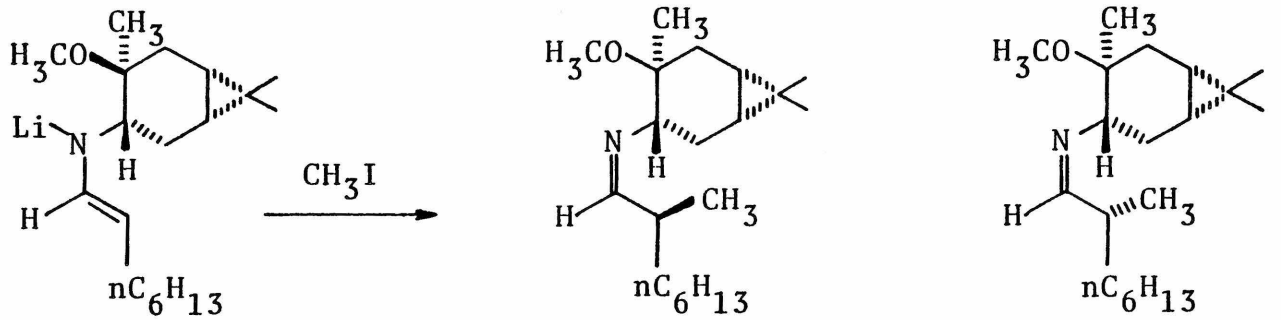
Ref. 9

Base (-23°/THF)	$R^1=CH_3$; R^2=hexyl A	B	Yield	R^1=hexyl; $R^2=CH_3$ A	B	Yield
LDA	69.5	30.5	70	74	26	48
LDA	75.5	24.5	60	--	--	--
LTMP	--	--	--	79	21	70
$KNEt_2$	51.9	48.1	13	--	--	--
LHMDS	--	--	--	69.5	30.5	9



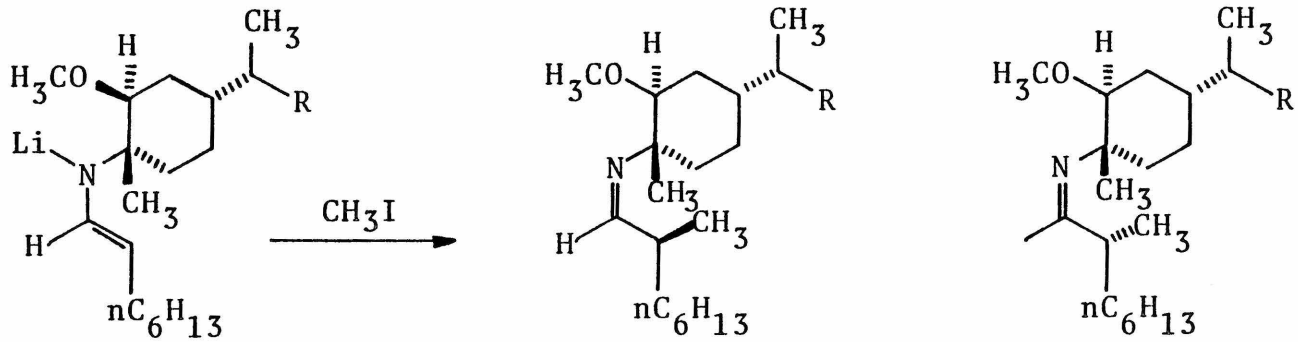
Ref. 10

R	R^1	Aldehydes		Yield
CH_3	CH_3	77.6	22.4	71
$=CH_2$	CH_3	87.6	12.4	60
$=CH_2$	$H_3COCH_2CH_2$	69	31	--



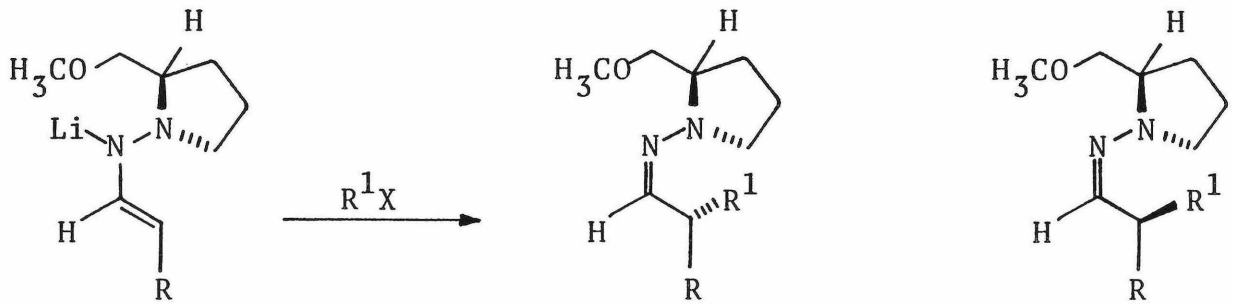
		Ref.
77	23	10

		Yield
77	23	57



R			Yield
CH_3	62.8	37.2	80
$=CH_2$	44.6	55.4	76

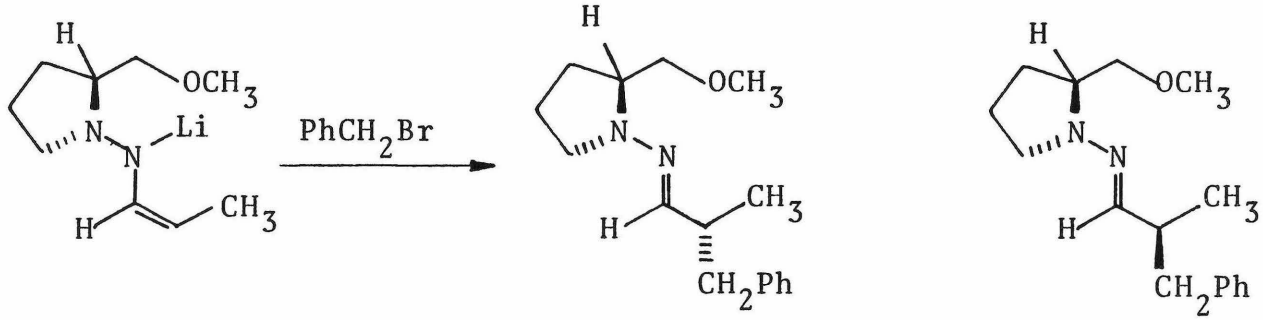
Ref.



11,12

Base[a]	R	R^1X	Aldehydes		Yield
A	CH_3	$PhCH_2Br$	91	9	62
B	CH_3	$PhCH_2Br$	92	8	--
A	CH_3CH_2	CH_3I	81	19	65
A	iC_3H_7	CH_3I	78.5	21.5	60
A	nC_6H_{13}	CH_3I	93.5	6.5	61
B	Ph	CH_3I	65.5	34.5	80

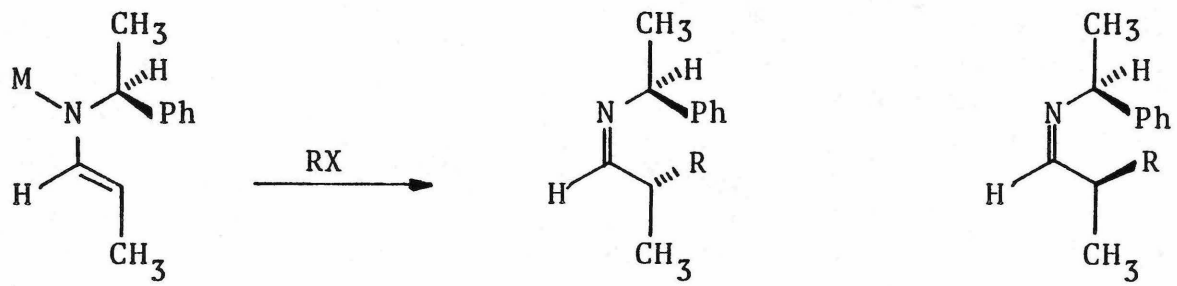
[a]Method A = $Li/HNEt_2/HMPA/PhH-THF/-10°/10$ h
Method B = LDA/THF/0°/7 h



12

58 42

(Used LDA/HMPA/THF as base)

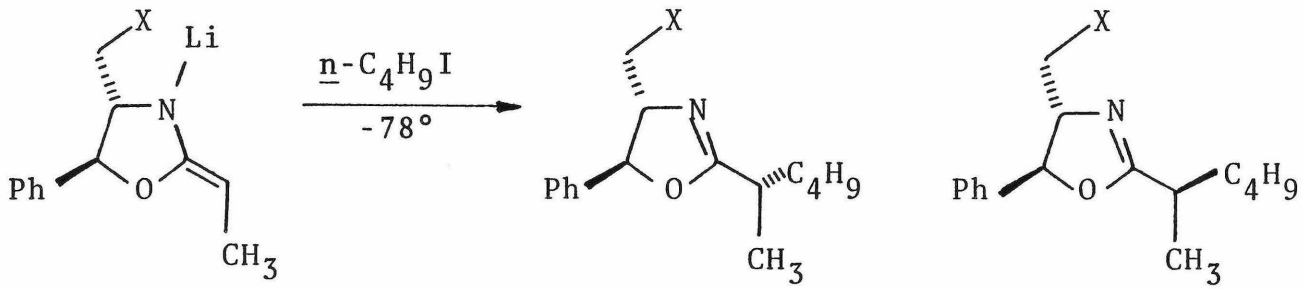


Ref.

6

M	R			Yield
Mg	$PhCH_2$	83.5	16.5	88
Mg	nC_6H_{13}	84.5	15.5	87
Li	iC_2H_7	85	15	85

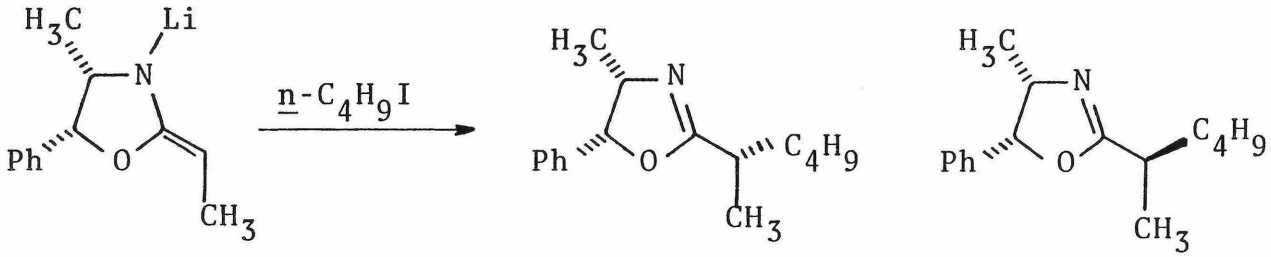
IV. CARBOXYLIC ACID DERIVATIVES



Ref. 13

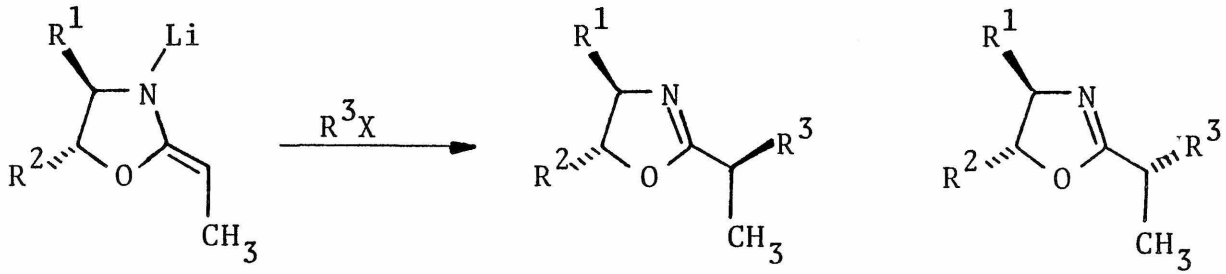
Oxazoline[a]	X	Acids		Yield
R	H	59	41	--
S	OLi	46.5	53.5	72
S	ONa	55	45	66
S	OCH_2CH_3	67.5	32.5	82
S	$OSiMe_3$	69	31	64
S	OCH_3	71.5	28.5	62

[a]Anion generates with n-BuLi/-78°/THF



35 65

Ref. 13

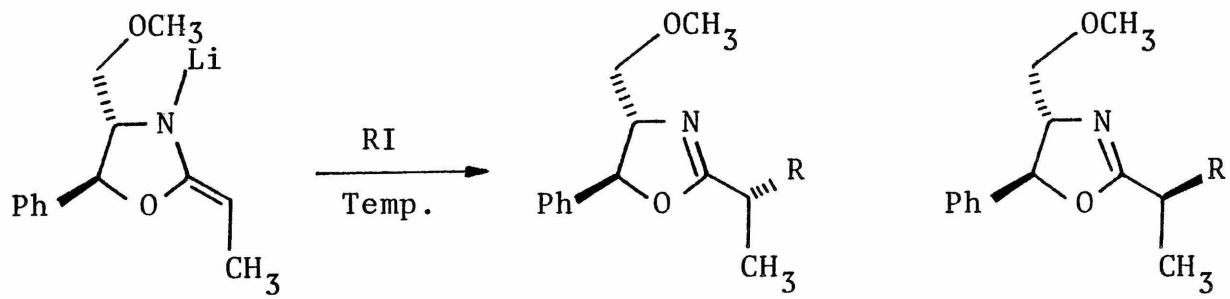


Ref.

14

R	R^2	R^3X			Yield
CH_2OCH_3	Ph	$PhCH_2Br$	87	13	--
CH_2OCH_3	CH_3	$PhCH_2Br$	73.6	26.4	--
CH_2OCH_3	H	$PhCH_2Br$	61.8	38.2	--
CH_2OCH_3	Ph	nC_4H_9I	89	11	--
CH_2OCH_3	CH_3	nC_4H_9I	53.6	46.4	--
CH_2OCH_3	H	nC_4H_9I	51.7	48.3	--
$C(CH_3)_2OCH_3$	H	nC_4H_9I	12.5	87.5	88

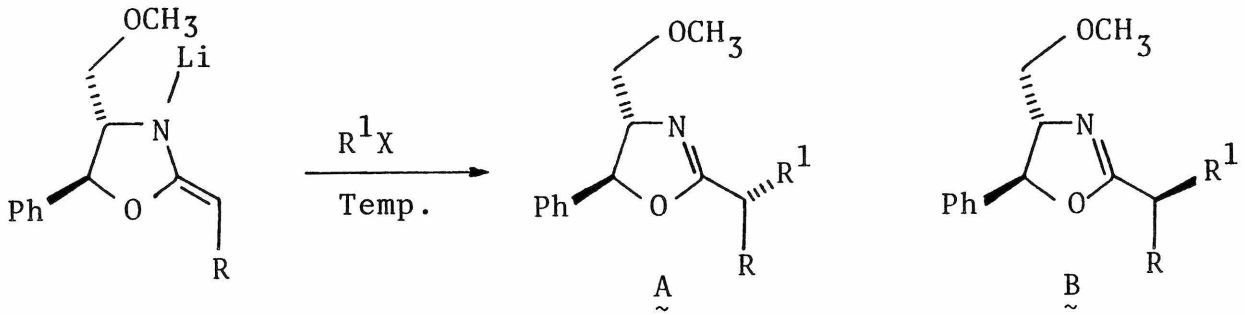
Ref.



13

R	Temp.	Acids	
nC_4H_9	-30	63.5	36.5
nC_4H_9	-45	72.5	27.5
nC_4H_9	-64	77	23
nC_4H_9	-78	83	17
nC_4H_9	-95	89	11
nC_4H_9	-105	88.5	11.5
nC_3H_7	-78	80	20
nC_3H_7	-105	86	14
C_2H_5	-78	84	16
C_2H_5	-105	92	8

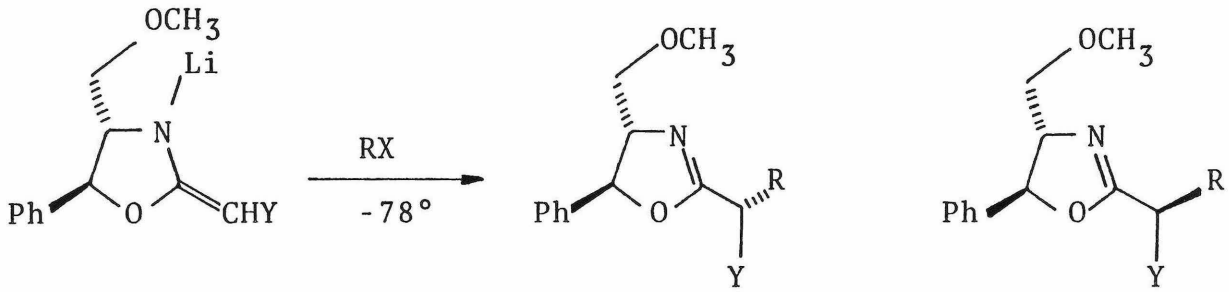
Ref.



13

R	R^1X	Temp.	A	B	Yield
CH_3	CH_3CH_2I	-98	89	11	84
CH_3	$CH_3CH_2CH_2I$	-98	86	14	79
CH_3	$CH_3CH_2CH_2CH_2I$	-78	87.5	12.5	65
CH_3	$PhCH_2Br$	-78	87	13	62
CH_3CH_2	$(CH_3)_2SO_4$	-98	89.5	10.5	83
CH_3CH_2	$PhCH_2Br$	-78	92.5	7.5	30
$CH_3CH_2CH_2$	$(CH_3)_2SO_4$	-98	86	14	74
$CH_2=CHCH_2$	$Me_3SiOCH_2CH_2I$	-98	93	7	--
$CH_3CH_2CH_2CH_2$	CH_3I	-78	60	40	--
$CH_3CH_2CH_2CH_2$	$(CH_3)_2SO_4$	-98	85	15	78
$CH_3CH_2CH_2CH_2$	$Me_3SiOCH_2CH_2I$	-98	88	12	--
$CH_3CH_2CH_2CH_2$	$PhCH_3Br$	-78	91	9	41
$Me_3SiOCH_2CH_2$	$(CH_3)_2SO_4$	-98	84.5	15.5	58
$Me_3SiOCH_2CH_2$	$CH_3CH_2CH_2I$	-98	86.5	13.5	75
$Me_3SiOCH_2CH_2$	$CH_2=CHCH_2Cl$	-98	86	14	60
$PhCH_2$	$(CH_3)_2SO_4$	-98	89	11	75
$PhCH_2$	CH_3CH_2I	-98	86.5	13.5	37
$PhCH_2$	$CH_3CH_2CH_2CH_2I$	-78	93	7	39
Ph	$(CH_3)_2SO_4$	-98	72.5	27.5	59
Ph	CH_3CH_2I	-98	75.5	24.5	42
Ph	$CH_3CH_2CH_2I$	-98	78	22	57
Ph	$CH_3CH_2CH_2CH_2I$	-78	76	24	38
Ph	iC_3H_7I	-63	82.5	17.5	22

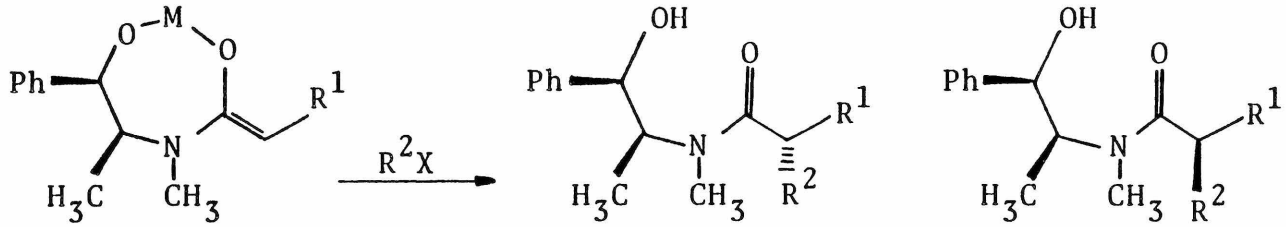
Ref.



15

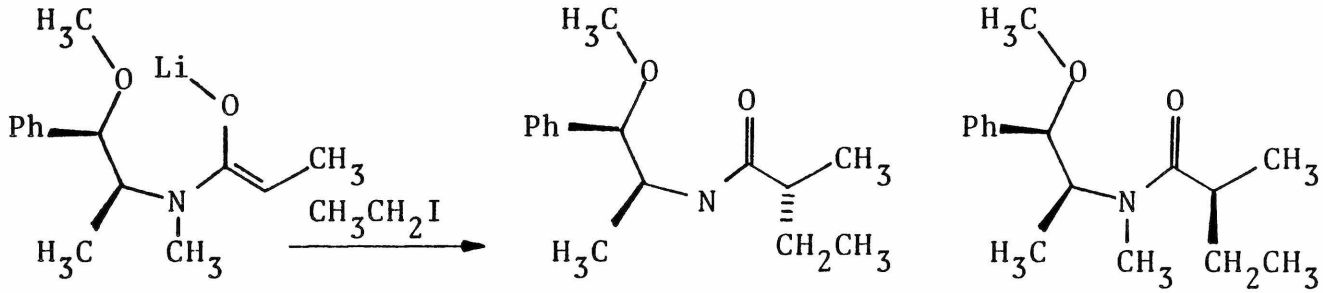
Y	R^1X	Acids		Yield
Cl	CH_3I	51	49	85
Cl	$(CH_3)_2SO_4$	51.5	48.5	90
Cl	CH_3CH_2I	55.5	44.5	90
Cl	$CH_3CH_2CH_2CH_2I$	64	36	94
OCH_3	CH_3I	44	56	93
OCH_3	$(CH_3)_2SO_4$	38.5	61.5	91
OCH_3	CH_3OTs	29	71	90
OCH_3	CH_3CH_2I	38.5	61.5	96
OCH_3	$(CH_3CH_2)_2SO_4$	34	66	91
OCH_3	$CH_3CH_2CH_2I$	39	61	95
OCH_3	$CH_3CH_2CH_2CH_2I$	39	61	97

Ref.



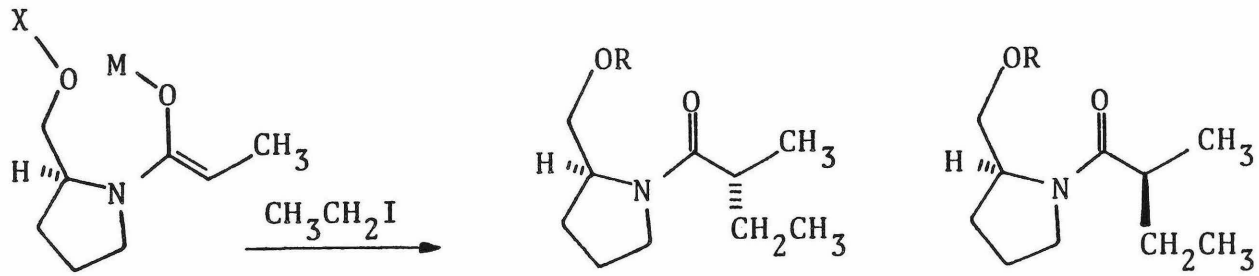
16

M	R^1	R^2X	Amides	
Li	CH_3	CH_3CH_2I	76	24
Mg	CH_3	CH_3CH_2I	95	5
Mg	CH_3	$CH_3CH_2CH_2CH_2I$	>95	5
Mg	CH_3CH_2	$CH_3CH_2CH_2CH_2I$	>90	10
Mg	CH_3CH_2	$PhCH_2I$	100	0



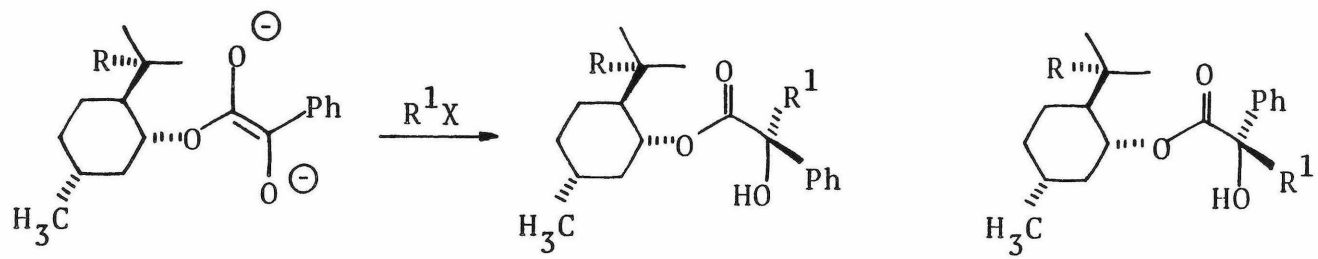
16

40 60



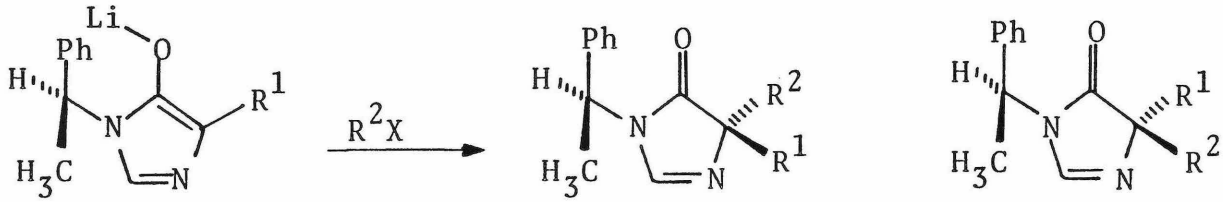
Ref. 17

X	R_1–	R_2–	Amides
CH_3	n-C_8H_{17}	CH_3	9:91
CH_3	n-C_8H_{17}	CH_3CH_2	9:91
Li	n-C_8H_{17}	CH_3	90:10
Li	n-C_8H_{17}	CH_3CH_2	84:16
Li	n-C_8H_{17}	n-C_4H_9	76:24
Li	CH_3	n-C_8H_{17}	83:17



18

R	R^1X	Esters		Yield
H	CH_3I	55	45	46
H	CH_3CH_2I	63.5	36.5	49
H	$CH_2{=}CHCH_2Br$	65.5	34.5	73
H	$CH_3CH_2CH_2CH_2Br$	75	25	32
H	$CH_3CH_2CH_2CH_2I$	70	30	75
H	$C_6H_{11}I$	53.5	46.5	68
H	$PhCH_2Br$	60	40	50
Ph	CH_3I	71	29	51
Ph	$CH_3CH_2CH_2CH_2I$	71.5	28.5	--

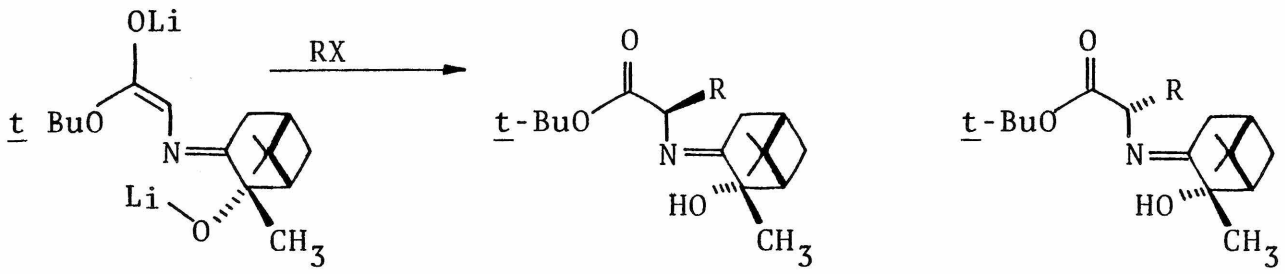


Ref.

19

R^1	R^2			Yield
CH_3	CH_2Ph	100	0	86
CH_3	CH_2-C_6H_3-3,4(OMe)	83	17	90
CH_3	CH_2-C_6H_3-4(OMe)	86	14	--
CH_3	CH_2-1-napthyl	>97	3	84
CH_3	CH_2-2-napthyl	>97	3	87
CH_3	CH_2-2-thienyl	>97	3	80
CH_3	CH_2-3-benzothienyl	>97	3	87
CH_3	CH_2-(2-bromo-3-benzofuranyl)	>97	3	88
CH_2CH_3	CH_2Ph	97.5	2.5	85
$CH_2CH{=}CH_2$	CH_2Ph	95	5	75
$CH_2CH_2CH_3$	CH_2Ph	95	5	77
iC_3H_7	CH_2Ph	97.5	2.5	78
$CH_2CH_2CH_2CH_3$	CH_2Ph	97.5	2.5	67
CH_2-C_6H_4-4Br	CH_2Ph	100	0	72
CH_2Ph	CH_3	60	40	89
CH_2Ph	CH_2-$CH{=}CH_2$	71.5	28.5	86
CH_2Ph	iC_3H_7	87.5	12.5	62
CH_2Ph	$CH_2CH_2CH_2CH_3$	75	25	72
CH_2Ph	CH_2CO_2Et	65.5	34.5	75
CH_2Ph	$CH_2C_6H_4$-4Br	100	0	87

Ref.



20

RX	Esters		Yield
CH_3I	91.5	8.5	52
iC_4H_9I	91.5	8.5	50
$PhCH_2Br$	86	14	79
$3,4(MeO)_2\text{-}C_6H_3CH_2Br$	83	17	62

References and Notes

(1) Literature data is tabulated in terms of diastereomer ratios. In cases where the authors did not analyze the diastereomeric mixture, the ratios are inferred from the enantiomeric purity of the final products.

(2) Meyers, A. I.; Williams, D. R.; Druelinger, M. J. Am. Chem. Soc. 1976, 98, 3032-3033.

(3) Whitesell, J. K.; Whitesell, M. A. J. Org. Chem. 1977, 42, 377-378.

(4) Worster, P. M.; McArthur, C. R.; Leznoff, C. C. Angew. Chem. Int. Ed. Engl. 1979, 18, 221-222.

(5) (a) Hashimoto, S. I.; Koga, K. Chem. Pharm. Bull. 1979, 27, 2760-2766. (b) Hashimoto, S. I.; Koga, K. Tetrahedron Lett. 1978, 573-576.

(6) Fraser, R. R.; Akiyama, F.; Banville, J. Tetrahedron Lett. 1979, 3929-3932.

(7) (a) Enders, D.; Eichenauer, H. Angew. Chem. Int. Ed. Engl. 1979, 18, 397-399. (b) Enders, D.; Eichenauer, H. Ibid 1976, 15, 549-551.

(8) Meyers, A. I.; Williams, D. R. J. Org. Chem. 1978, 43, 3245-3247.

(9) Meyers, A. I.; Poindexter, G. S.; Brich, Z. J. Org. Chem. 1978, 43. 902=898.

(10) (a) Meyers, A. I.; Brich, Z.; Erickson, G. W.

J. Chem. Soc., Chem. Commun. 1979, 566-567. (b) Meyers, A. I.; Brich, Z. Ibid 1979, 567-568.

(11) (a) Enders, D.; Eichenauer, H. Chem. Ber. 1979, 112, 2933-2960. (b) Enders, D.; Eichenauer, H. Tetrahedron Lett. 1977, 191-194.

(12) Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. J. Am. Chem. Soc. 1979, 101, 5654-5659.

(13) (a) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. J. Am. Chem. Soc. 1976, 98, 567-576. (b) Meyers, A. I.; Mihelich, E. D. J. Org. Chem. 1975, 40, 1186-1187. (c) Meyers, A. I.; Mihelich, E. D. Angew. Chem. Int. Ed. Engl. 1976, 15, 270-281. (d) Meyers, A. I. Pure & Appl. Chem. 1979, 51, 1255-1268.

(14) (a) Meyers, A. I.; Mazzu, A.; Whitten, C. E. Heterocycles 1977, 6, 971-977. (b) Hansen, J. F.; Cooper, C. S. J. Org. Chem. 1976, 41, 3219-3220.

(15) Meyers, A. I.; Knaus, G.; Kendall, P. M. Tetrahedron Lett. 1974, 3495-3498.

(16) (a) Larcheveque, M.; Ignatova, E.; Cuvigny, T. J. Organomet. Chem. 1979, 177, 5-15. (b) Larcheveque, M.; Ignatova, E.; Cuvigny, T. Tetrahedron Lett. 1978, 3961-3964.

(17) Sonnet, P. E.; Heath, R. R. J. Org. Chem. 1980, 45, 3139-3141.

(18) Kaneko, T.; Turner, D. L.; Newcomb, M.; Bergbreiter, D. E. Tetrahedron Lett. 1979, 103-106.

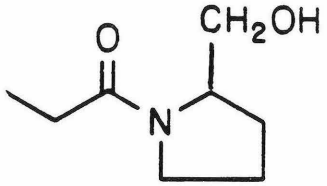
(19) Yamada, S.-I.; Oguri, T.; Shioiri, T. J. Chem. Soc., Chem. Commun. 1976, 136-137.

(20) Schöllkopf, U.; Hartwig, W.; Groth, U. Angew. Chem. Int. Ed. Engl. 1979, 18, 863-864.

VII. APPENDIX II

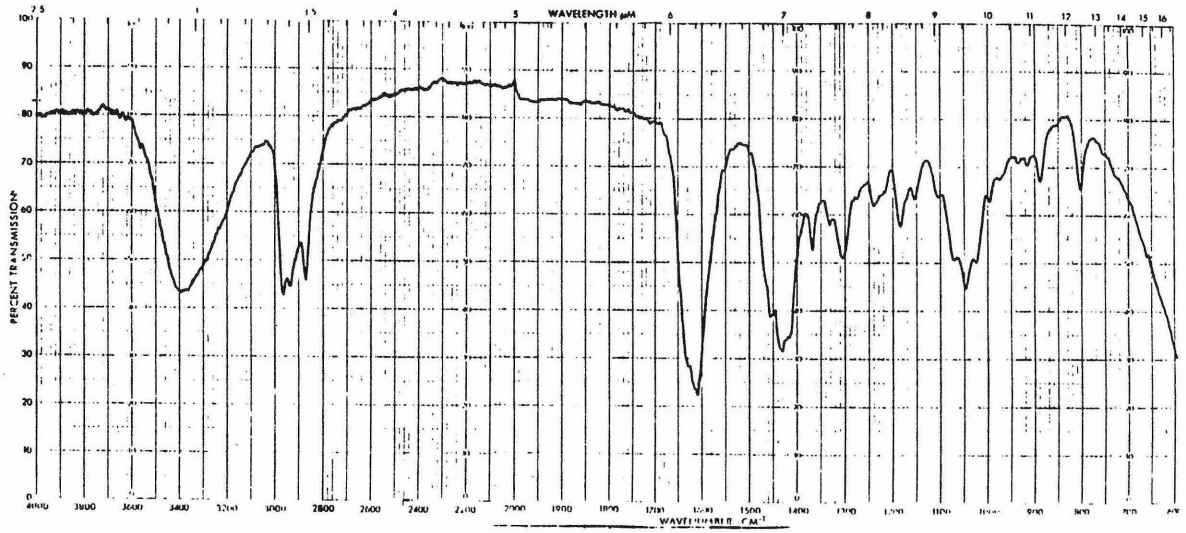
IR, ^{1}H NMR and ^{13}C NMR Spectral Catalog

Page 87

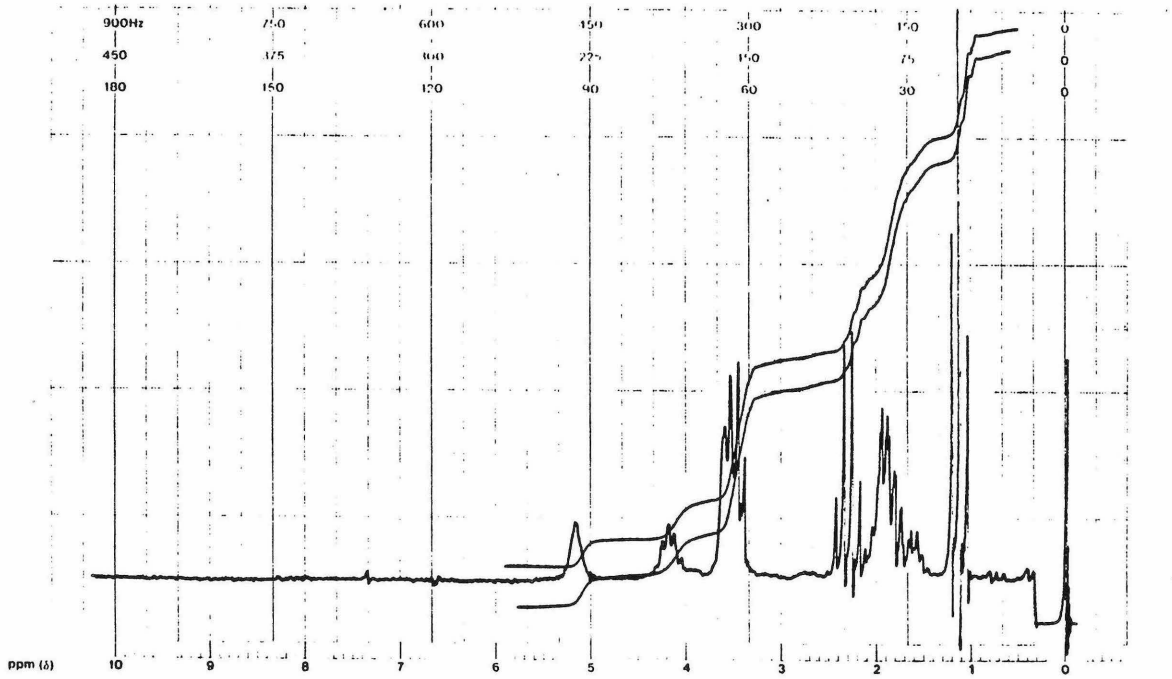


15

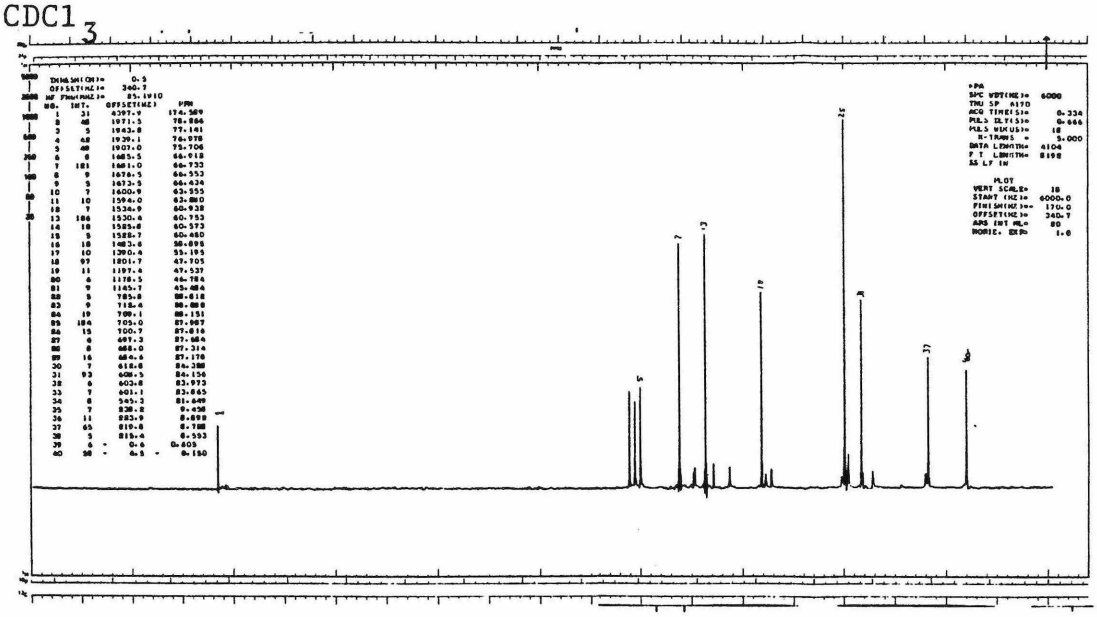
Neat



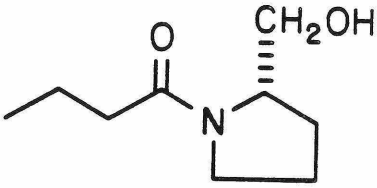
$CDCl_3$



$CDCl_3$

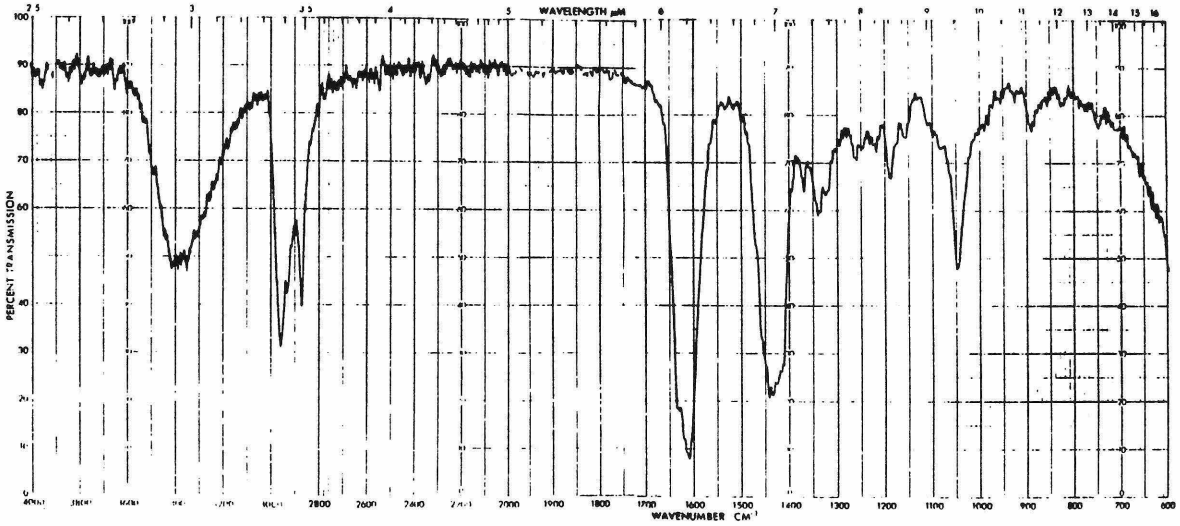

DWELL SH(CR)= 0.5
OFFSET(HZ)= 340.7
NF FREQ(HZ)= 85.1910
NO. INT. OFFSET(HZ) PPM
1 31 4397.9 174.589
2 48 1971.5 78.886
3 5 1943.8 77.141
4 48 1920.1 76.978
5 48 1907.0 75.706
6 8 1685.5 66.918
7 181 1681.0 66.733
8 9 1676.5 66.552
9 5 1673.5 66.434
10 7 1600.9 63.555
11 10 1594.0 63.280
12 7 1534.9 60.938
13 184 1530.4 60.753
14 18 1585.8 60.573
15 5 1588.7 60.480
16 18 1483.8 58.895
17 10 1390.4 55.195
18 97 1301.7 47.705
19 11 1197.4 47.537
20 6 1178.5 46.784
21 7 1165.7 45.484
22 5 785.8 31.818
23 9 718.4 28.888
24 19 709.1 28.151
25 184 705.0 27.987
26 15 700.7 27.816
27 6 697.3 27.684
28 8 688.0 27.314
29 16 684.6 27.178
30 7 618.8 24.388
31 93 608.5 24.156
32 6 603.8 23.973
33 7 601.1 23.865
34 8 545.3 21.649
35 7 238.8 9.458
36 11 223.9 8.888
37 65 218.8 8.788
38 5 215.4 8.593
39 6 - 0.6 - 0.803
40 38 - 4.5 - 0.150
PPM
SPC WDT(HZ)= 6000
TRU SP AVTO
ACQ TIME(S)= 0.334
PULS DLY(S)= 0.666
PULS WID(US)= 18
R-TRANS = 5.000
DATA LENGTH= 4104
F T LENGTH= 8192
AS LF IN
PLOT
VERT SCALE= 18
START (HZ)= 6000.0
FINISH(HZ)= 170.0
OFFSET(HZ)= 340.7
ARS INT MU= 80
NORM. EXP= 1.0

Page 88

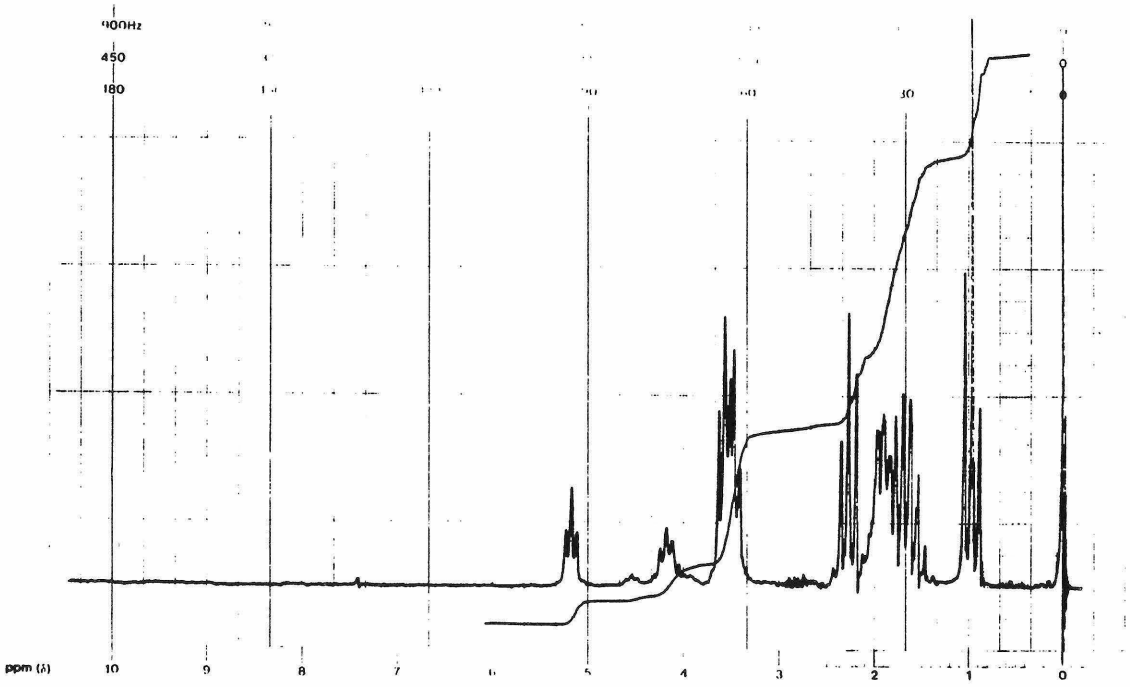


Neat

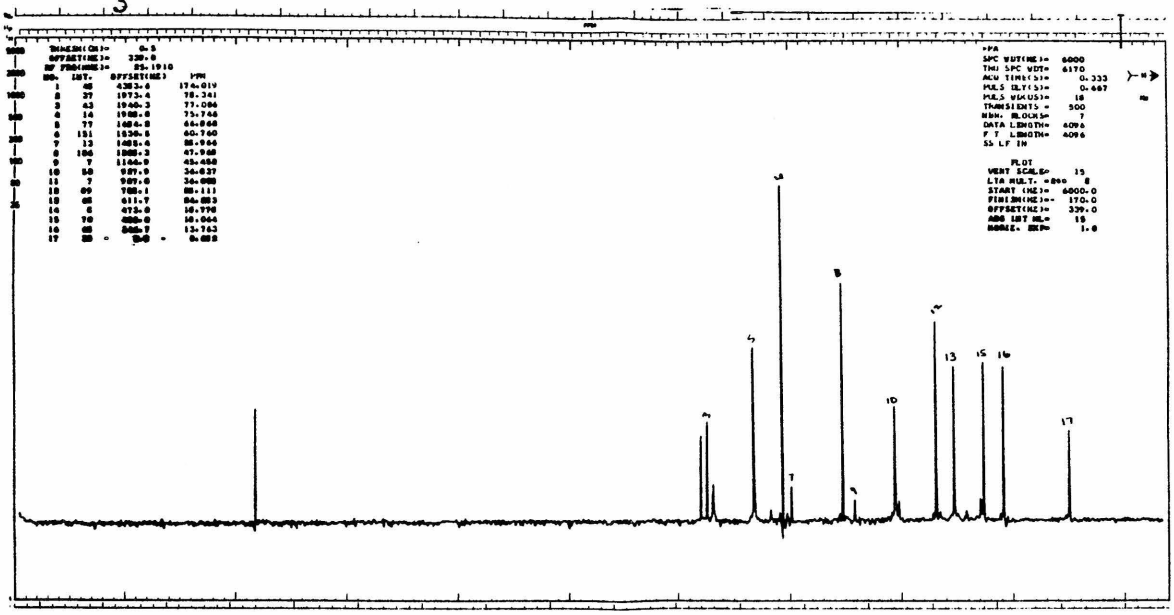
16



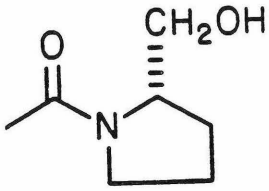
$CDCl_3$



$CDCl_3$

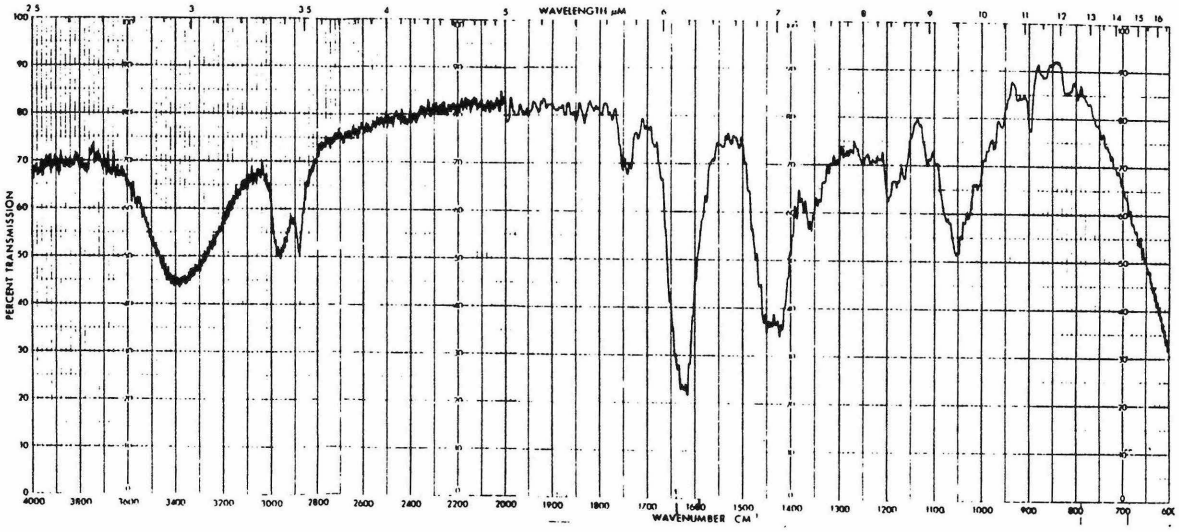

SPC WDT(HZ)= 6000
THU SPC WDT= 6170
ACU TIME(S)= 0.333
PULS DLY(S)= 0.667
PULS WID(US)= 18
TRANSIENTS = 500
NUM. BLOCKS= 7
DATA LENGTH= 4096
F T LENGTH= 4096
SS LF IN
PLOT
VERT SCALE= 15
LTA MULT. =800 8
START (HZ)= 6000.0
FINISH(HZ)= 170.0
OFFSET(HZ)= 339.0
ADD INT MUL= 15
NORMLZ. EXP= 1.0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

Page 88

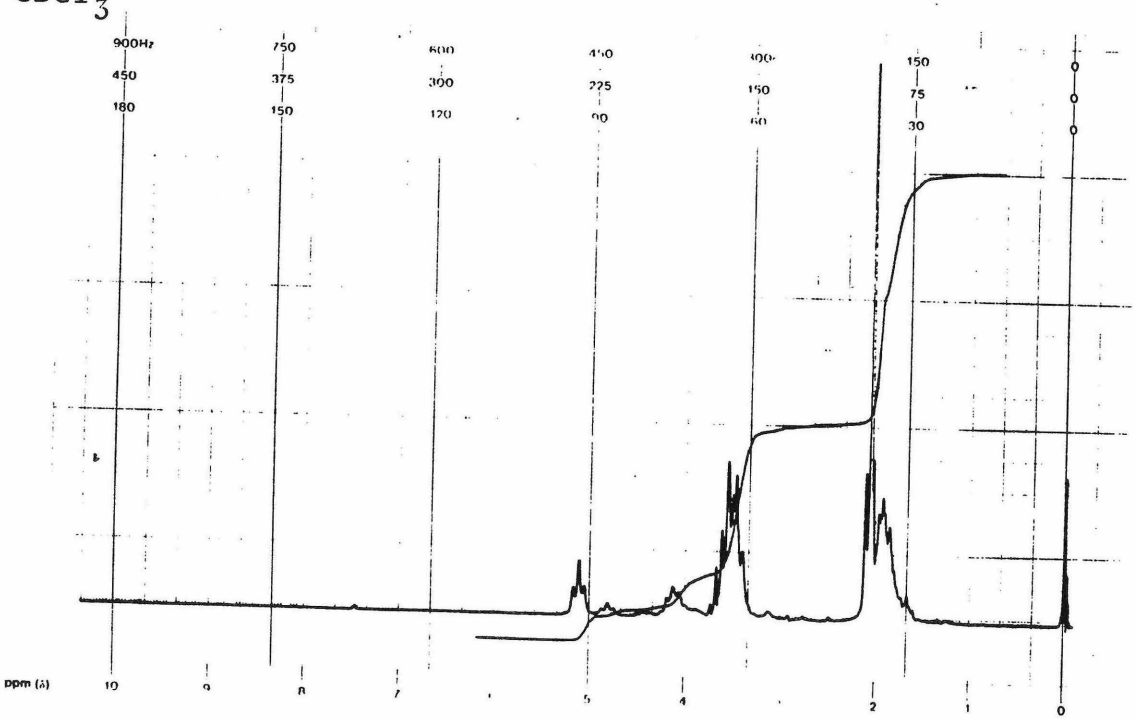


20

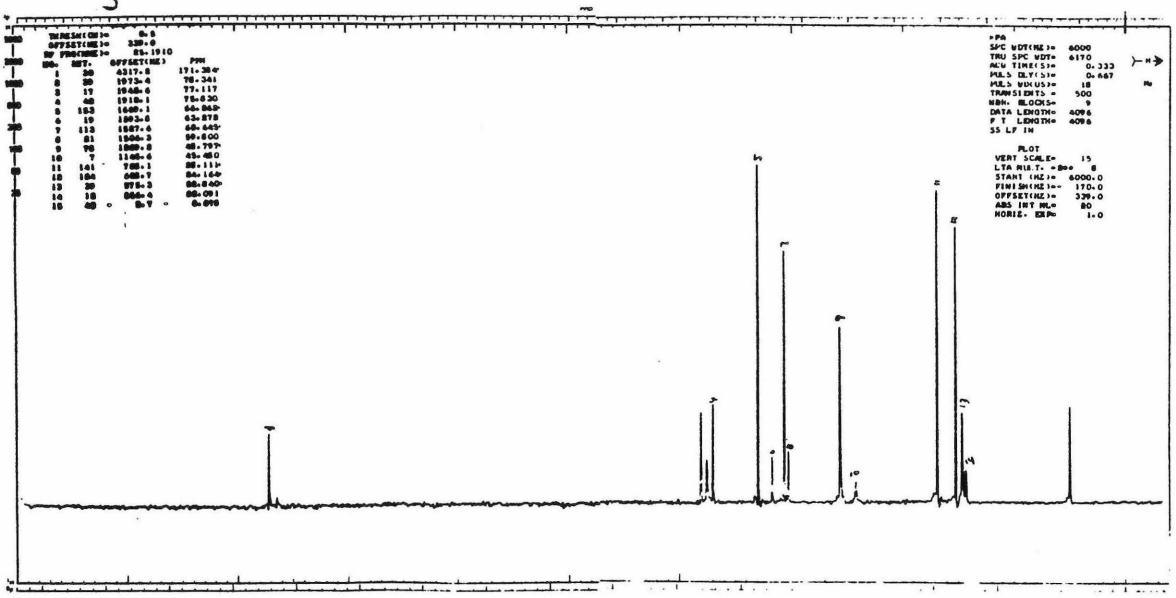
Neat



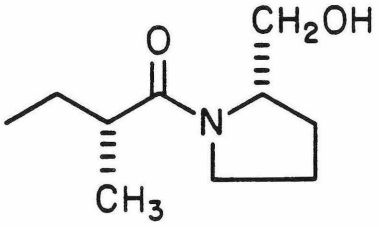
$CDCl_3$



$CDCl_3$

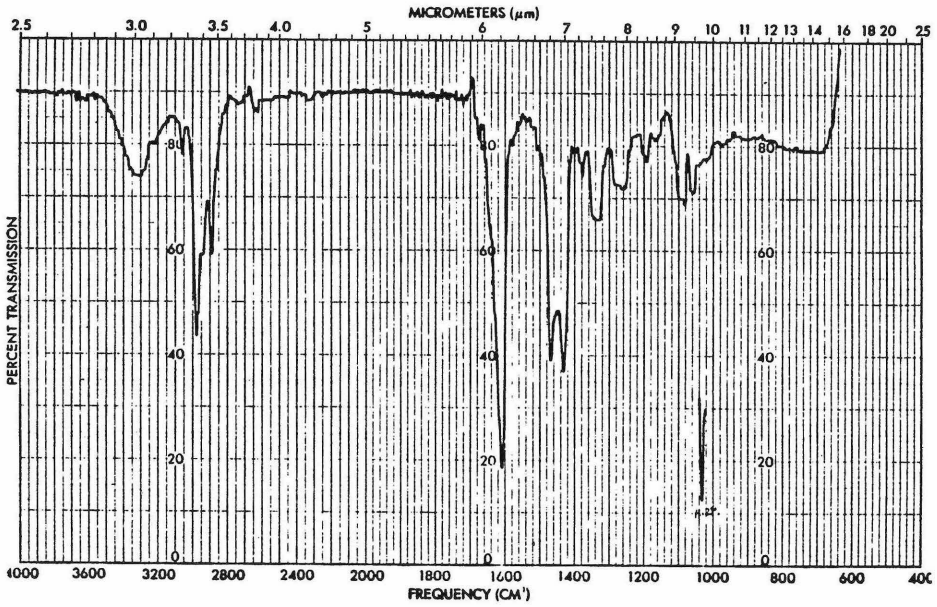


Page 91

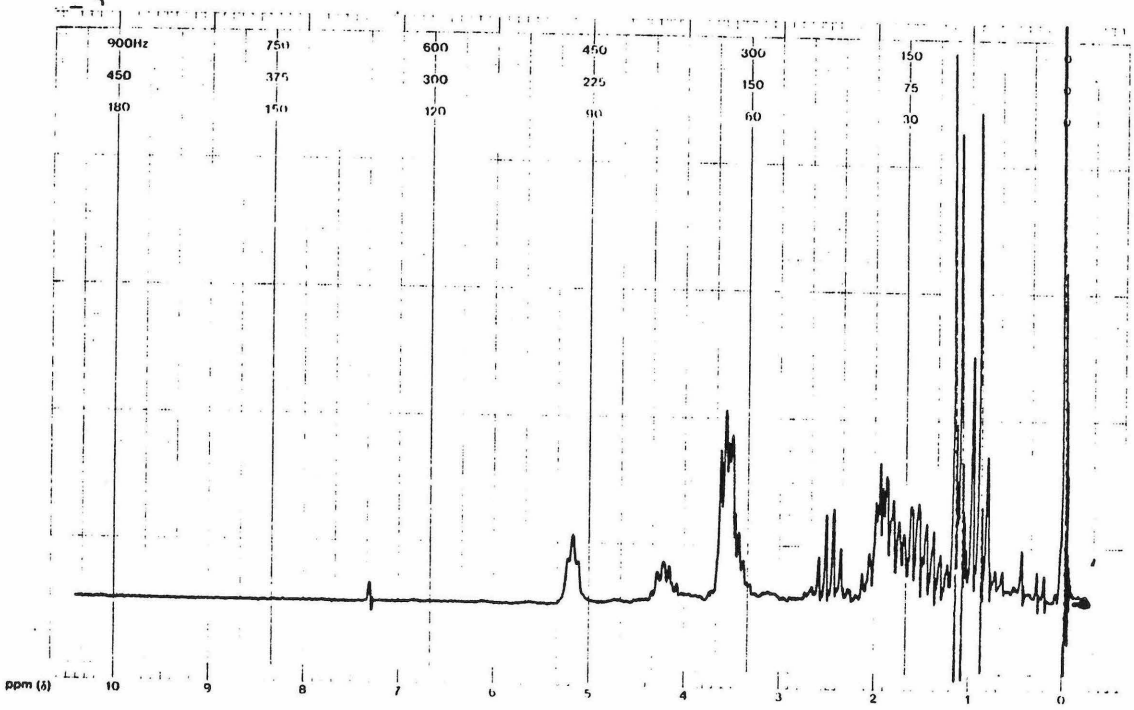


28

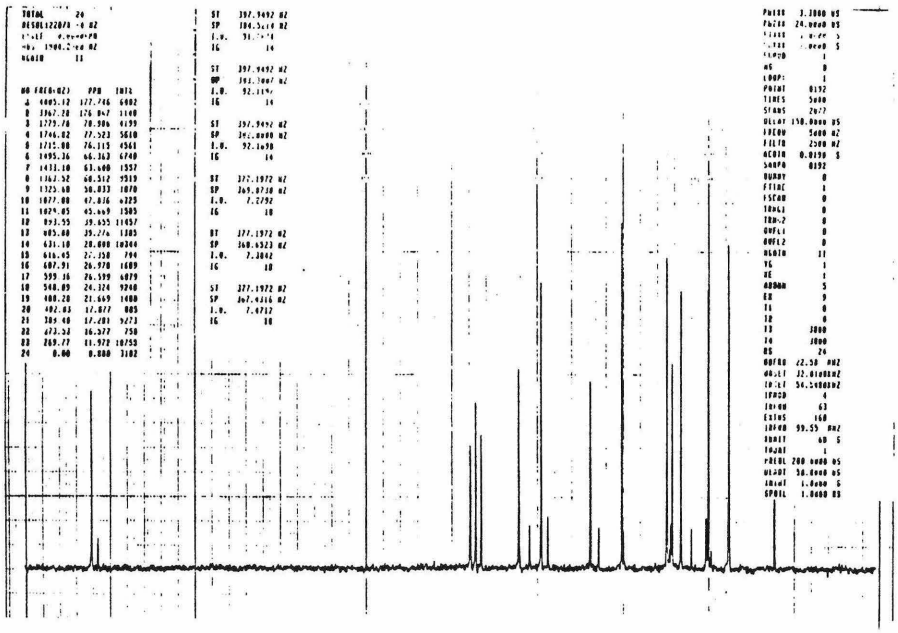
CCl_4



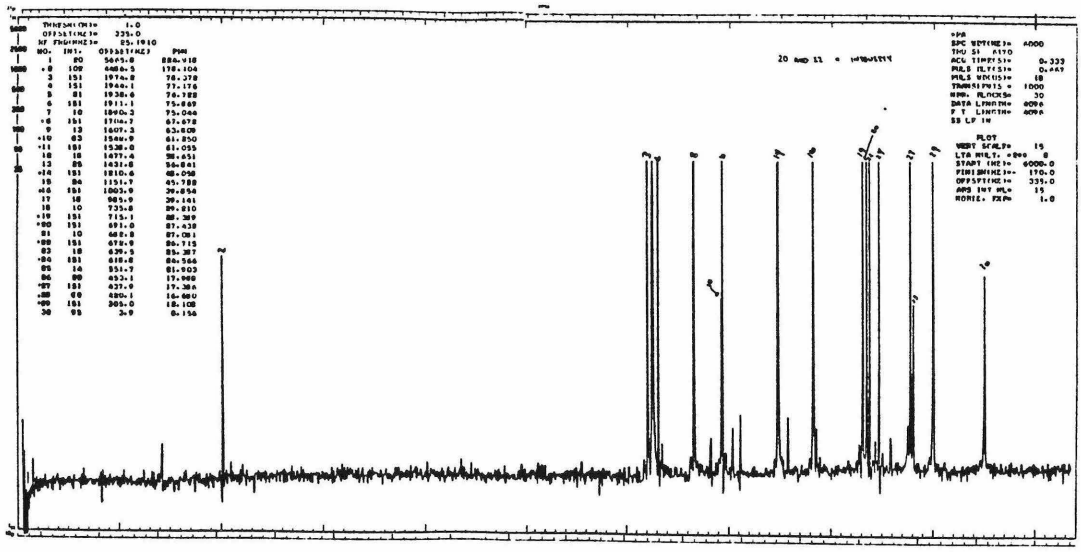
$CDCl_3$



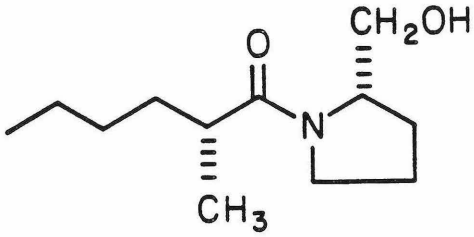
$CDCl_3$



$CDCl_3$ (authentic mixture)

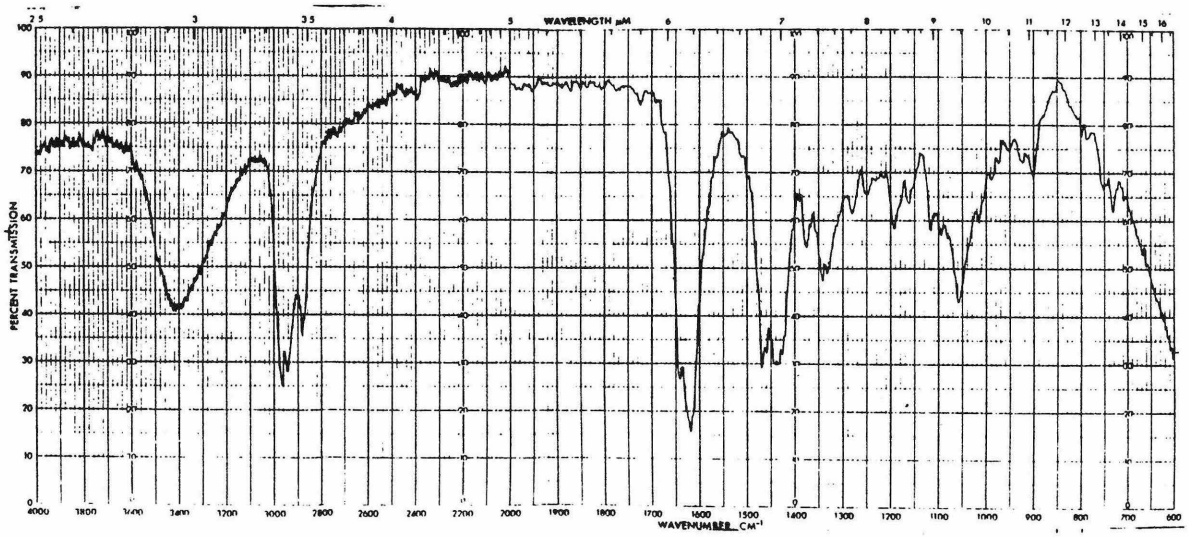


Page 93

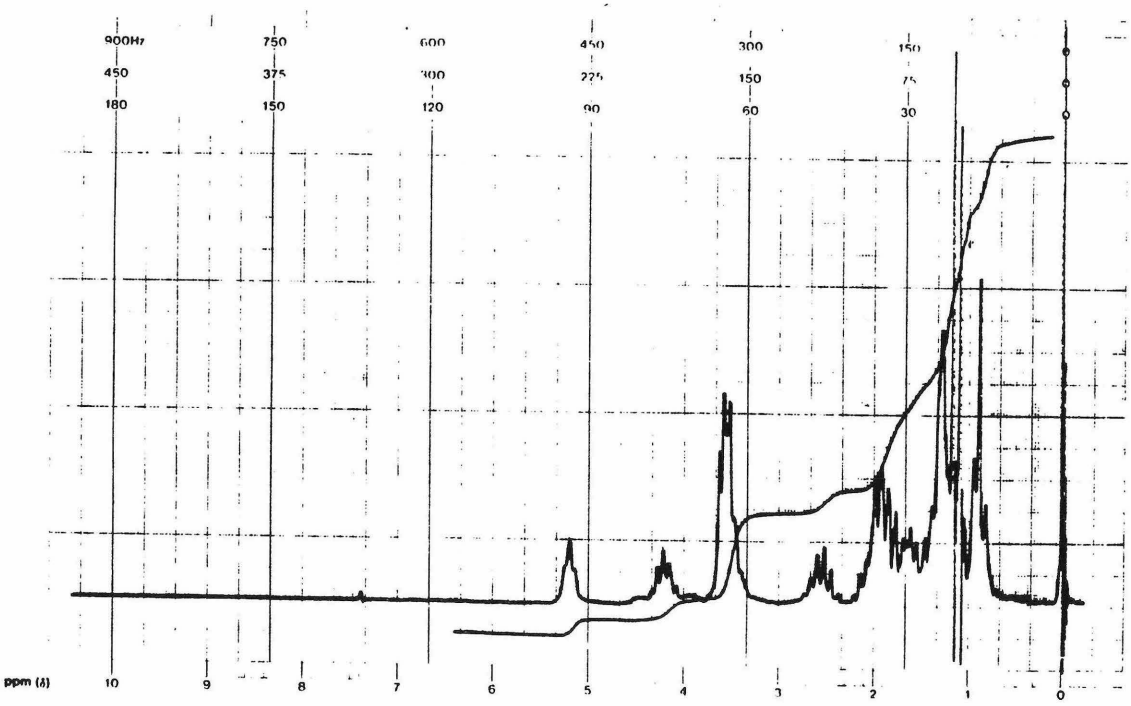


Neat

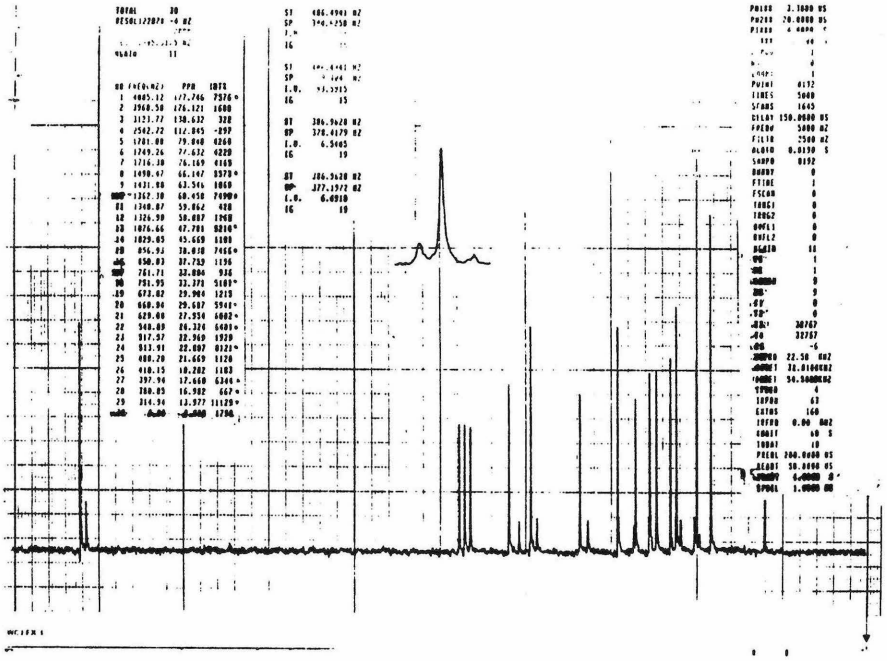
44



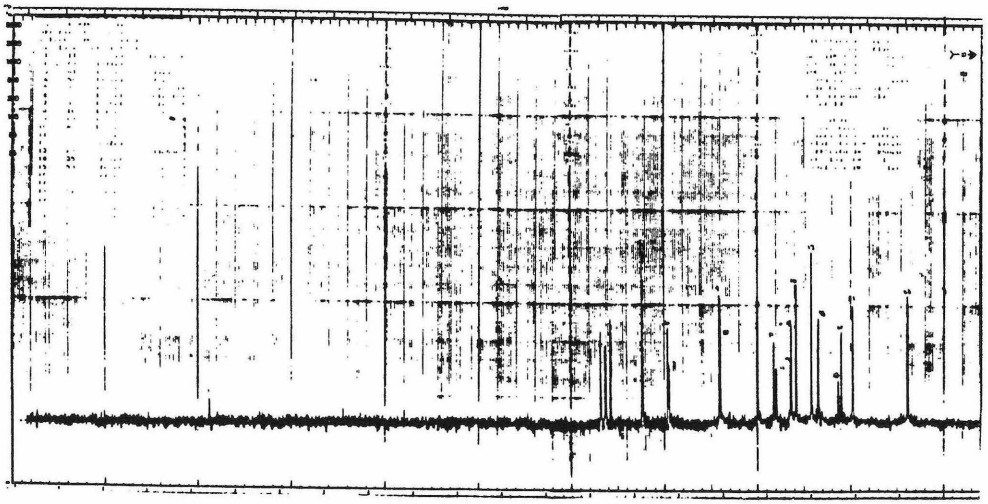
$CDCl_3$



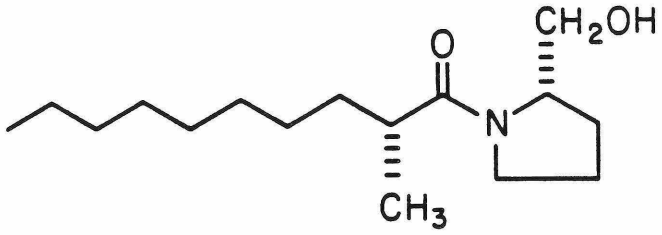
$CDCl_3$



$CDCl_3$ (authentic mixture)

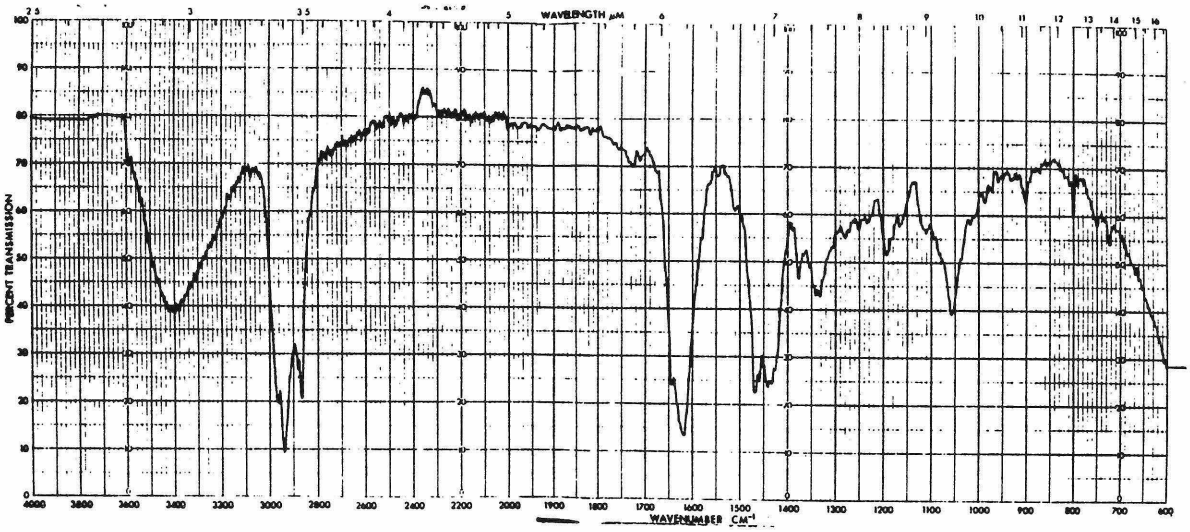


Page 94

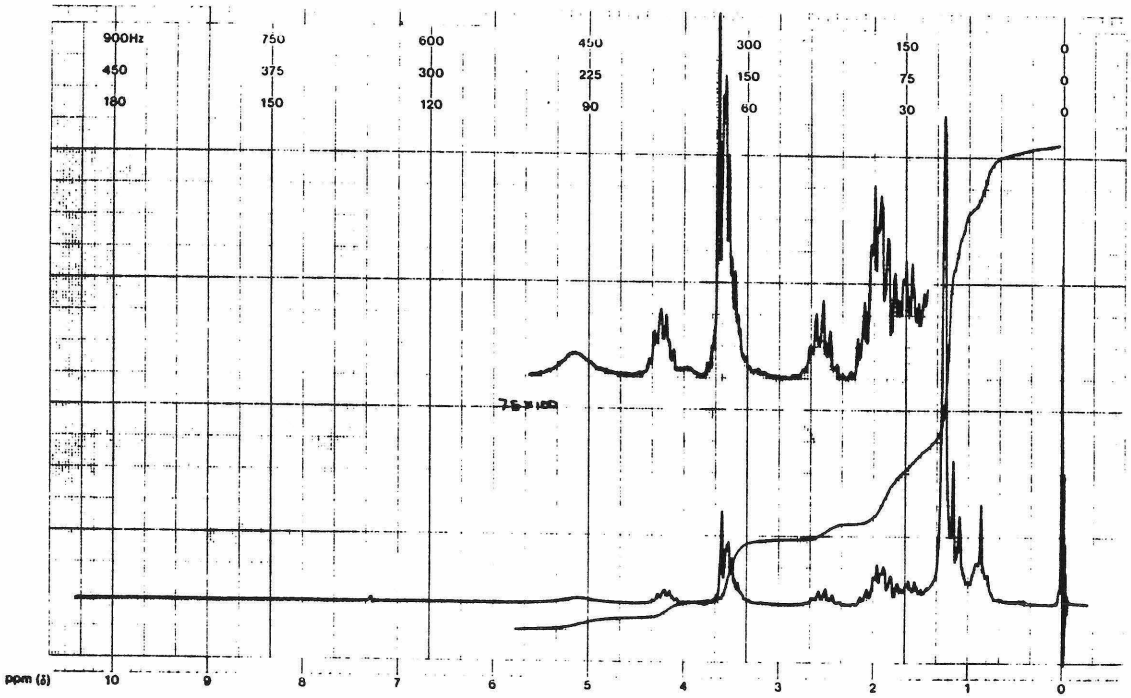


45

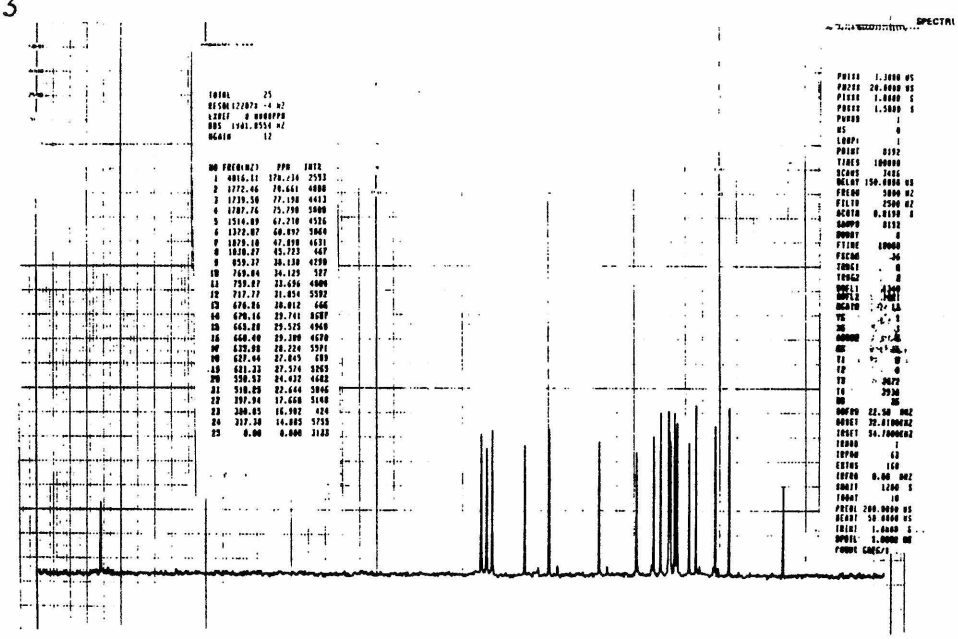
Neat



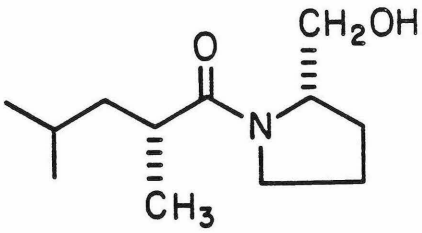
$CDCl_3$



$CDCl_3$

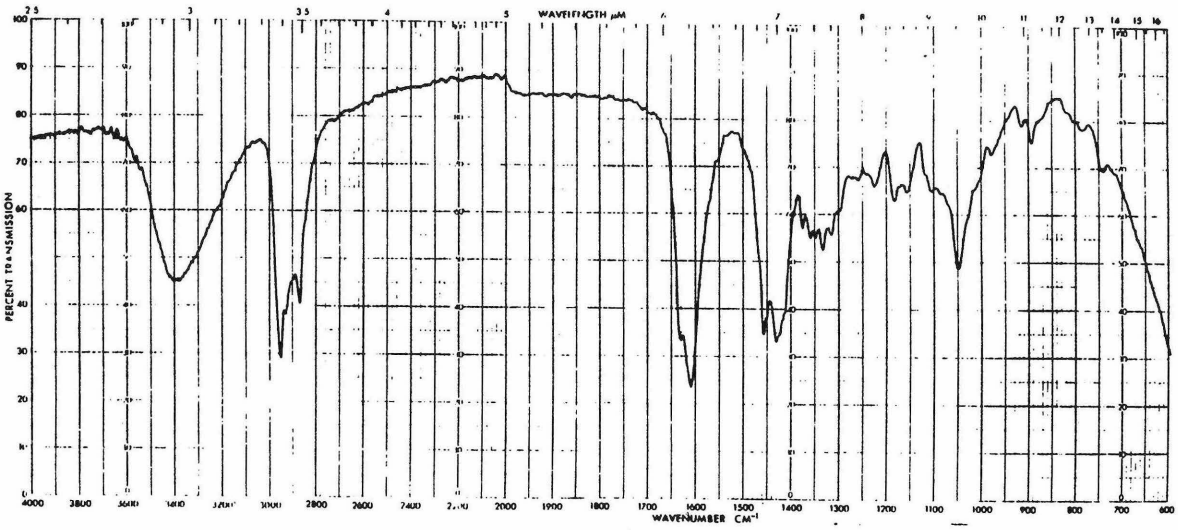

SPECTRU
TOTAL 25
NO FREQ(HZ) PPM INTE
1 4016.11 170.214 2593
2 1772.46 70.661 4080
3 1719.50 77.198 4413
4 1707.76 75.790 5900
5 1514.09 67.210 4526
6 1372.87 60.892 5060
7 1273.10 67.898 4631
8 1020.27 45.723 447
9 959.27 38.138 4290
10 769.04 34.129 587
11 757.27 33.636 4009
12 717.77 31.854 5592
13 676.16 30.012 666
14 670.16 29.741 8687
15 663.28 29.525 4960
16 660.40 29.300 4670
17 639.98 28.224 5571
18 627.64 27.845 [illegible]
19 601.23 27.574 5265
20 550.53 24.432 4682
21 510.05 22.644 5046
22 397.94 17.660 5140
23 380.05 16.902 424
24 317.38 14.085 5755
25 0.00 0.000 3183
PW1X 1.3000 US
PW2X 20.0000 US
PX1X 1.0000 S
PX2X 1.5000 S
PWXD 1
US 0
LOOP1 1
POINT 8192
TIMES 100000
SCANT 2456
DELAY 150.0000 US
FREQD 5000 HZ
FILTR 2500 HZ
ACQTM 0.8190 S
SAMPD 8192
DUMMY 0
FIRE 10000
FECHO 36
TONE1 0
TONE2 0
TONE3 4500
DWFL1 .500
ACQTD 0.1 LB
TE 1 S
TI 0
TP 0
TD 2072
TG 2930
NO 25
OBFRQ 22.50 MHZ
OBSET 32.8190MHZ
IRSET 54.7000MHZ
IRNUM 1
IRPWR 63
IRTOS 160
IRFRQ 0.00 MHZ
SDELT 1200 S
TOGGT 10
PECHO 200.0000 US
RCAST 50.0000 US
IDIM 1.0000 S
SPOTL 1.0000 DB
FOURT CAECYL

Page 95

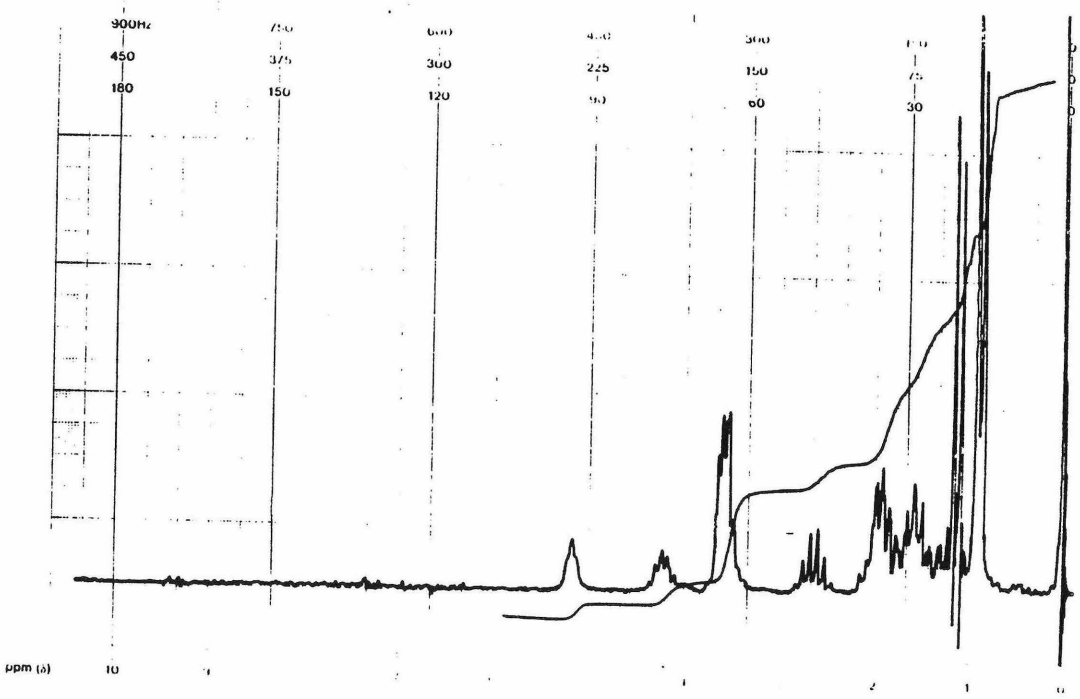


Neat

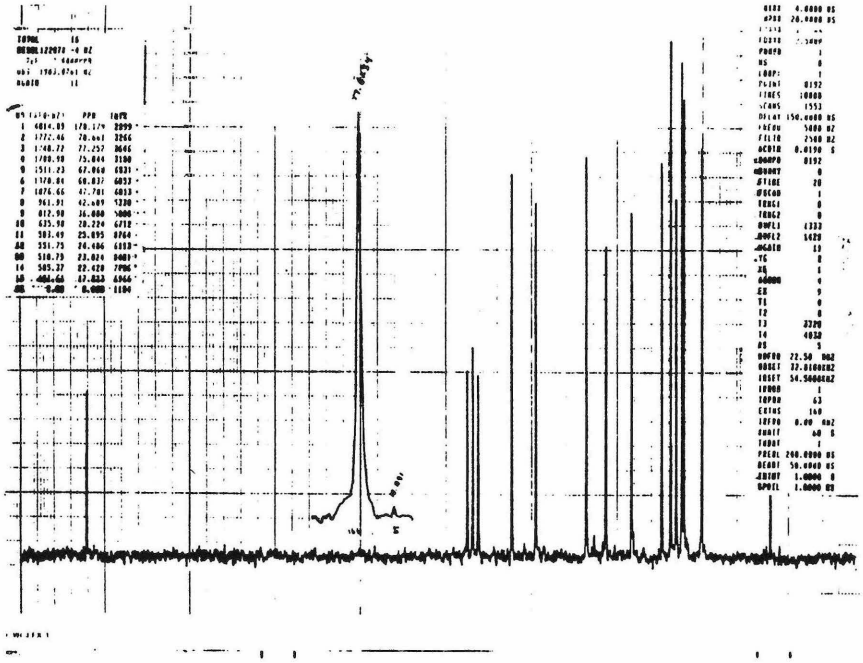
12



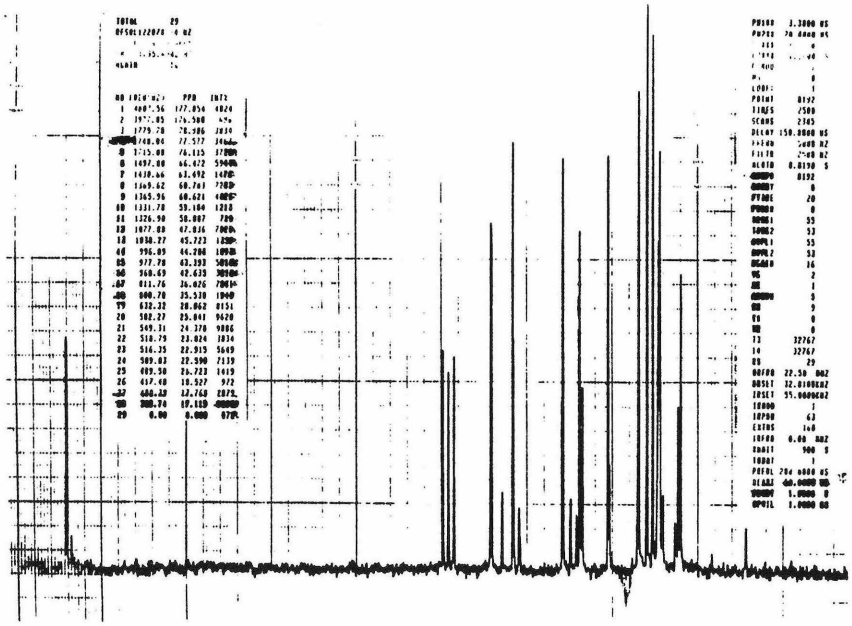
$CDCl_3$



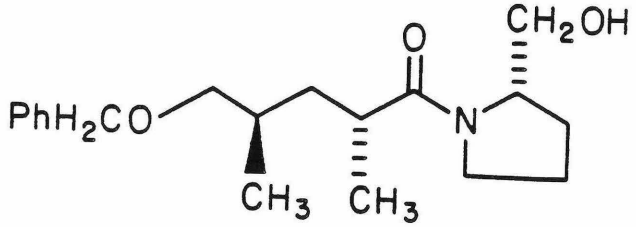
$CDCl_3$



$CDCl_3$ (authentic mixture)

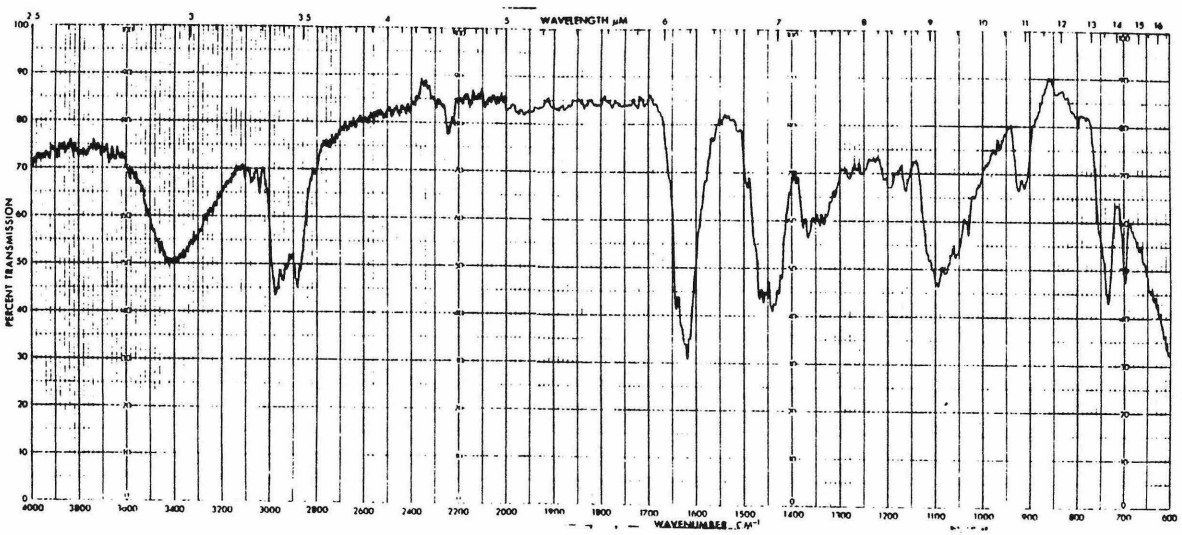


Page 97

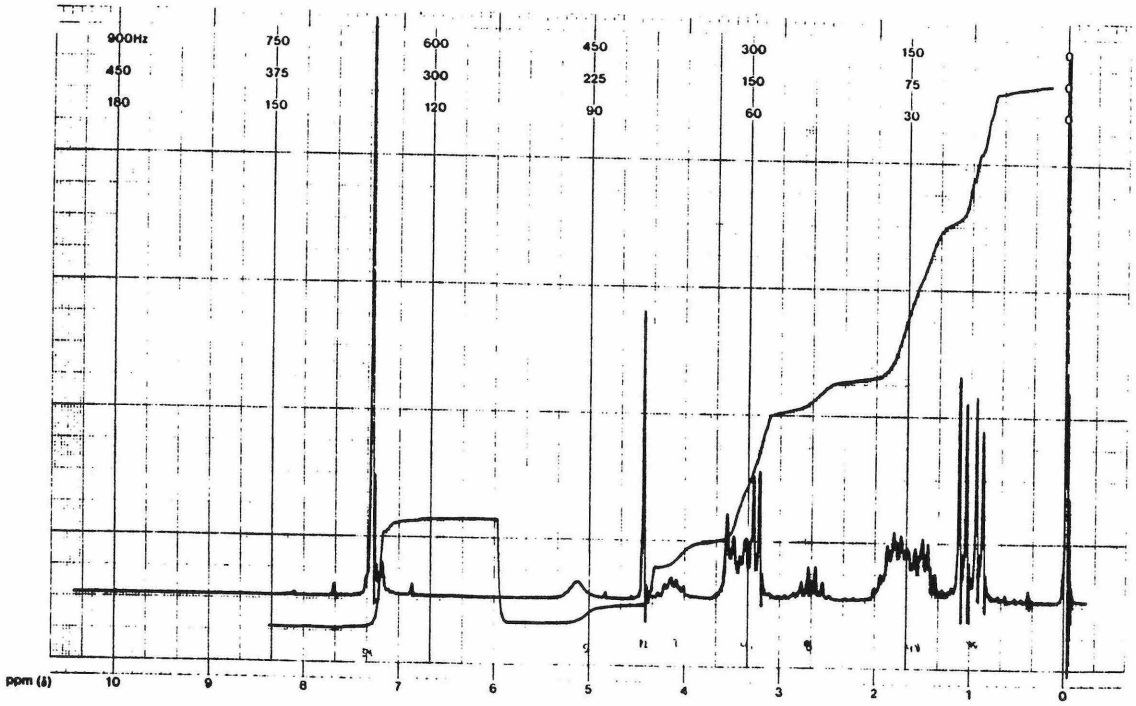


Neat

47

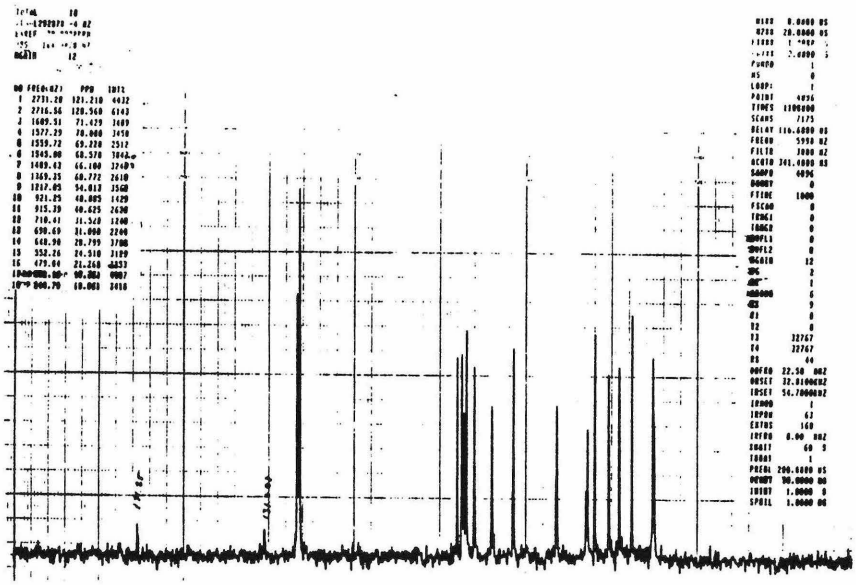


$CDCl_3$

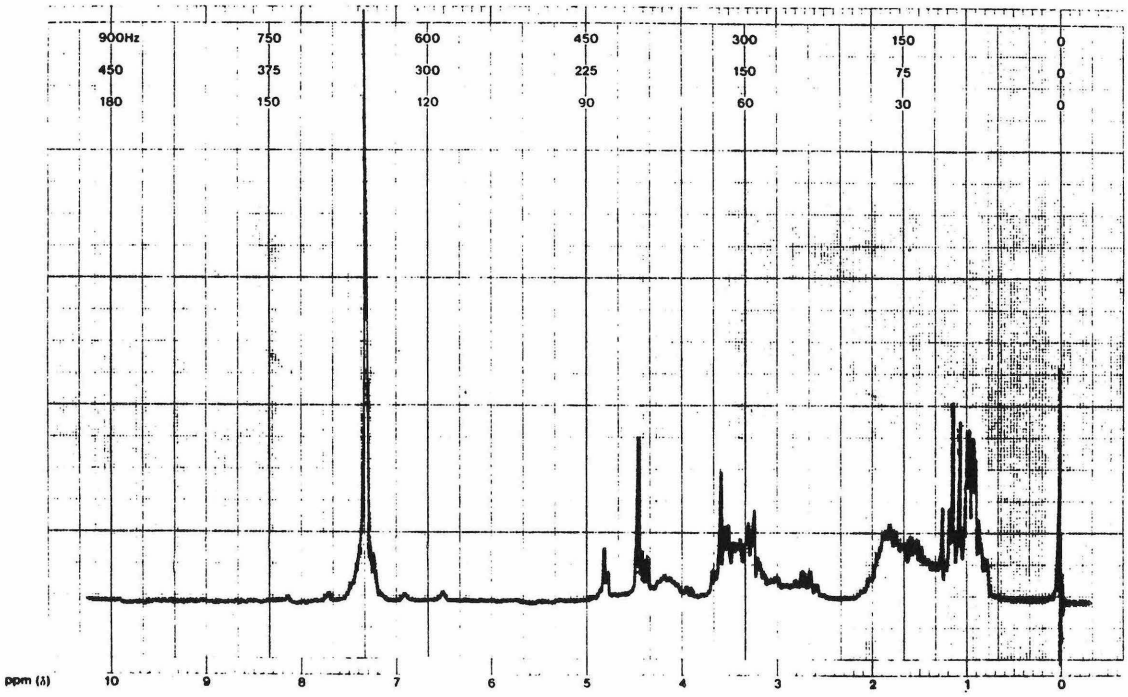


Page 97

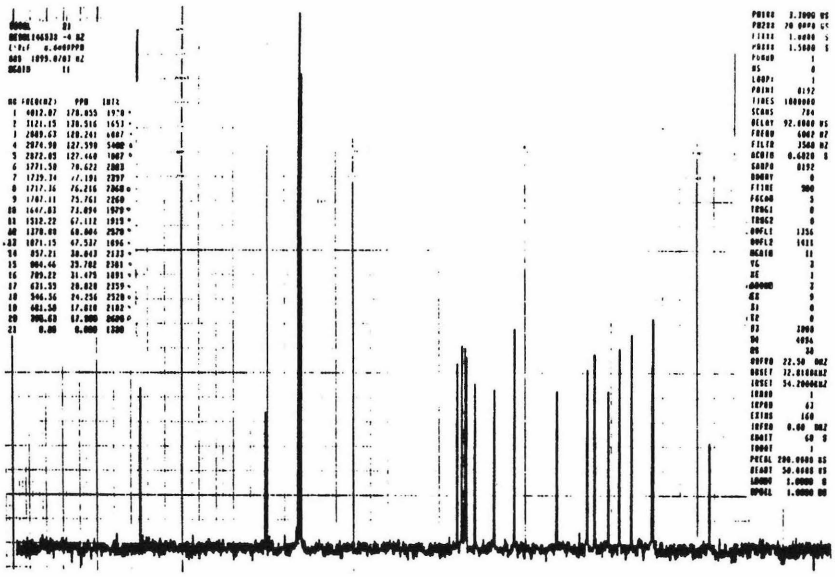
$CDCl_3$ (authentic mixture)



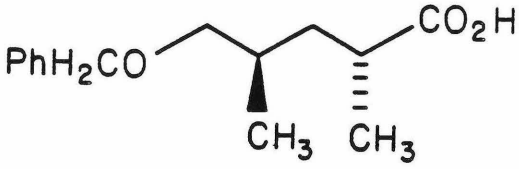
$CDCl_3$ (authentic mixture)



$CDCl_3$

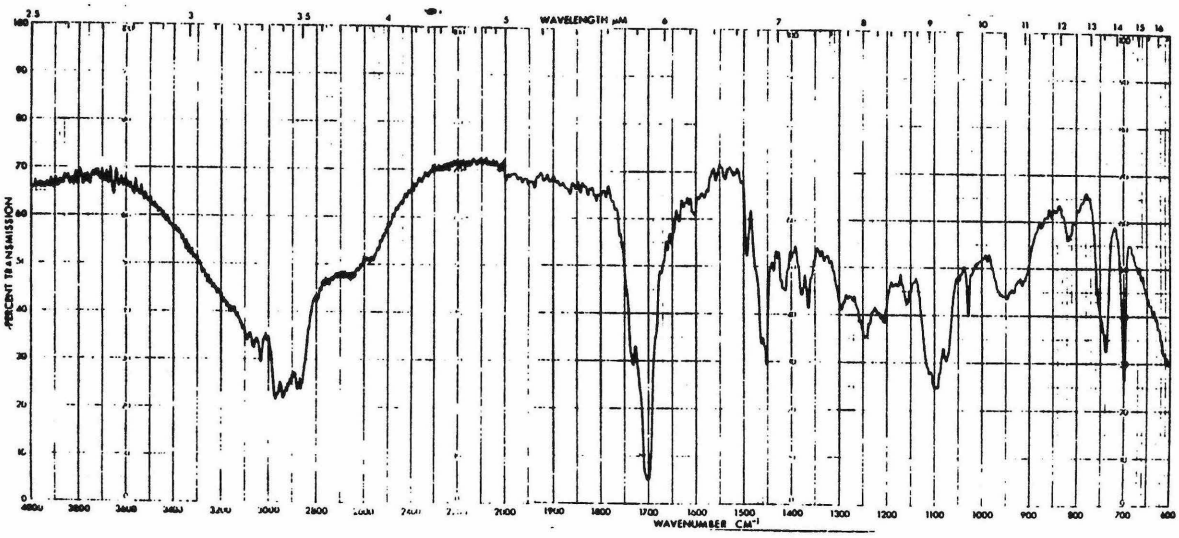


Page 98

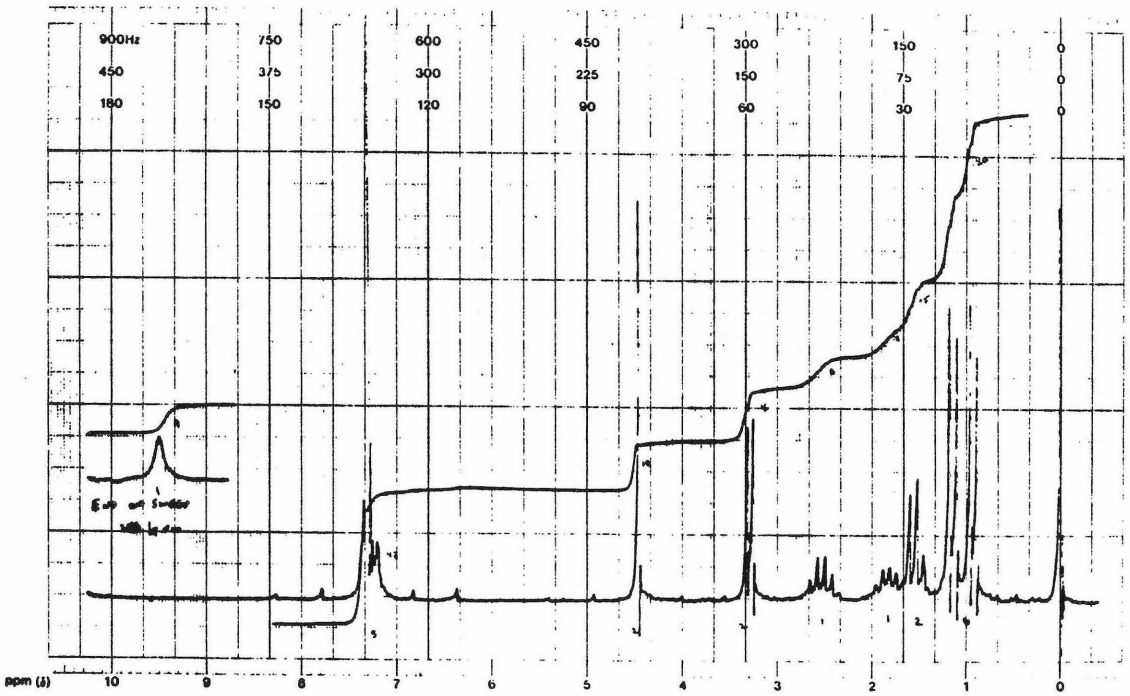


Neat

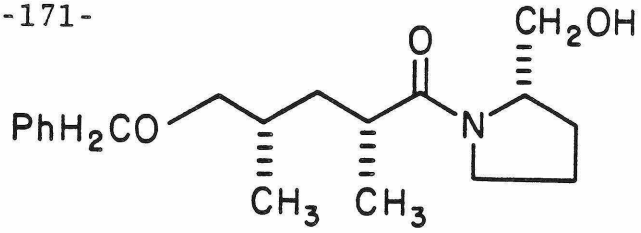
48



$CDCl_3$

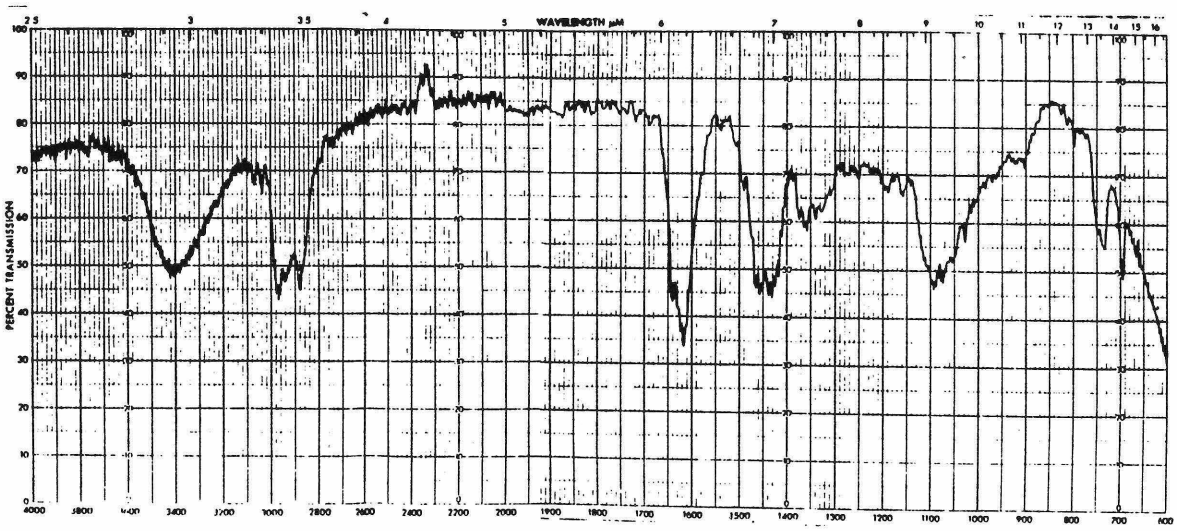


Page 98

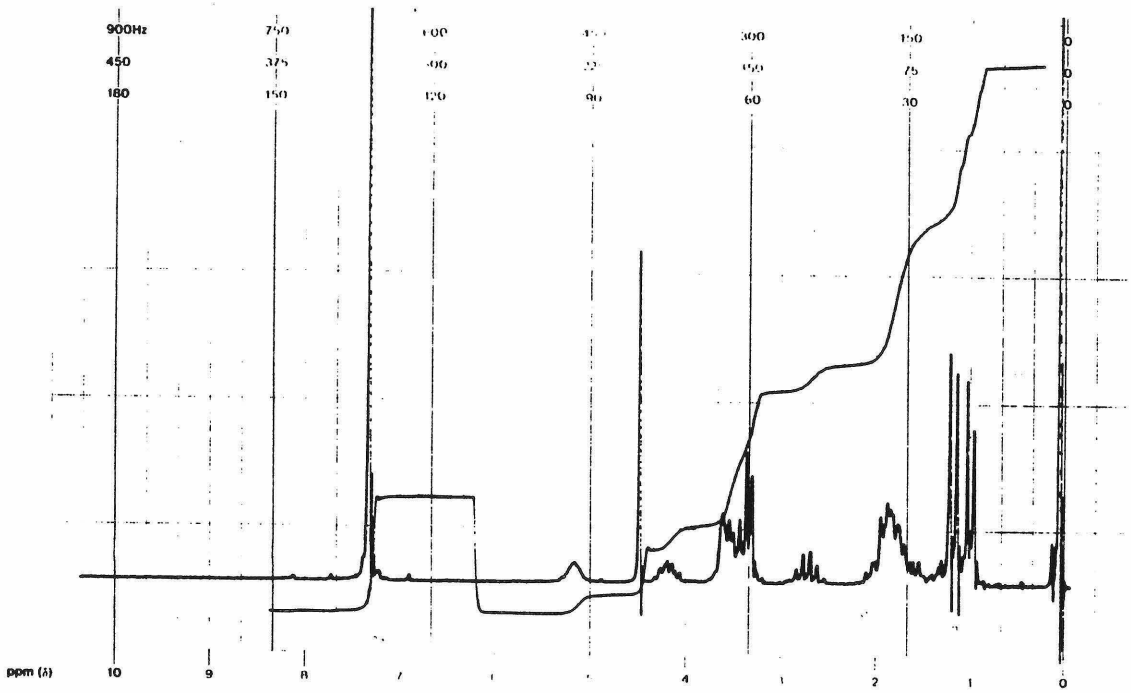


Neat

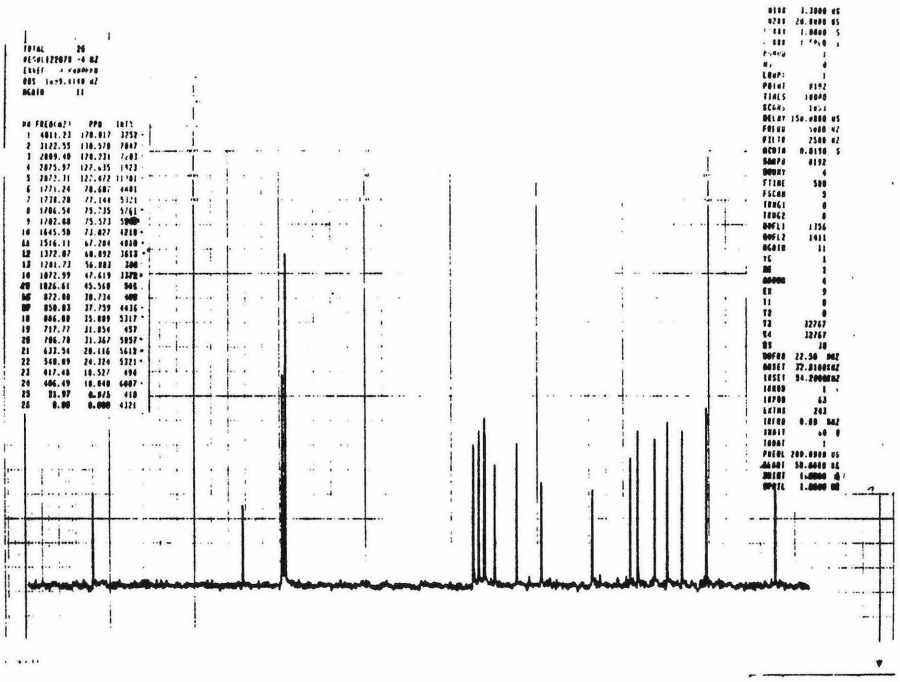
49



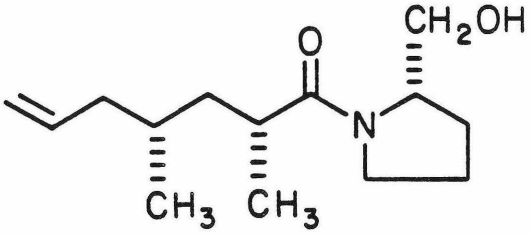
$CDCl_3$



$CDCl_3$

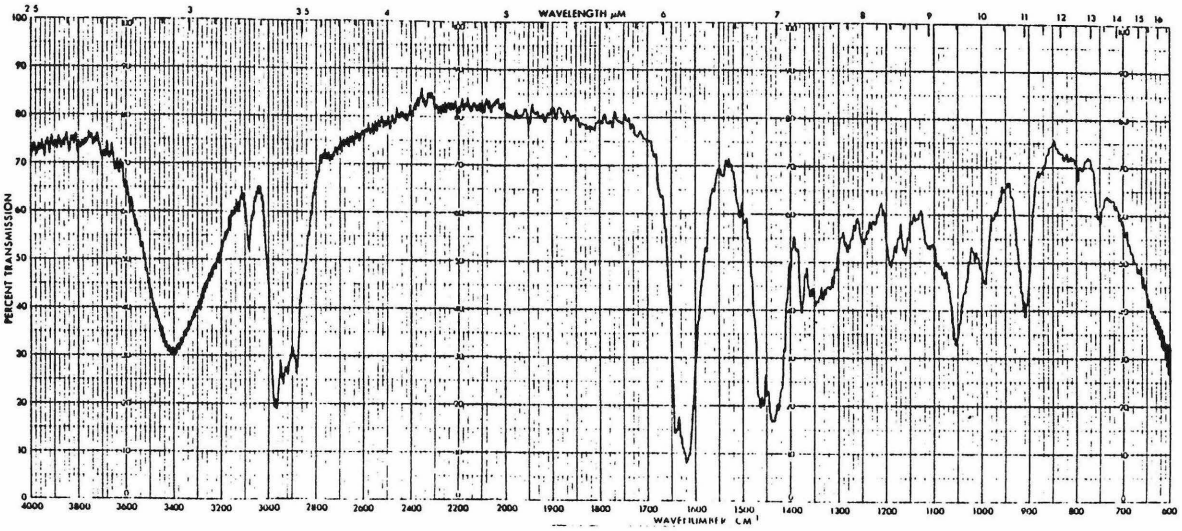


Page 99

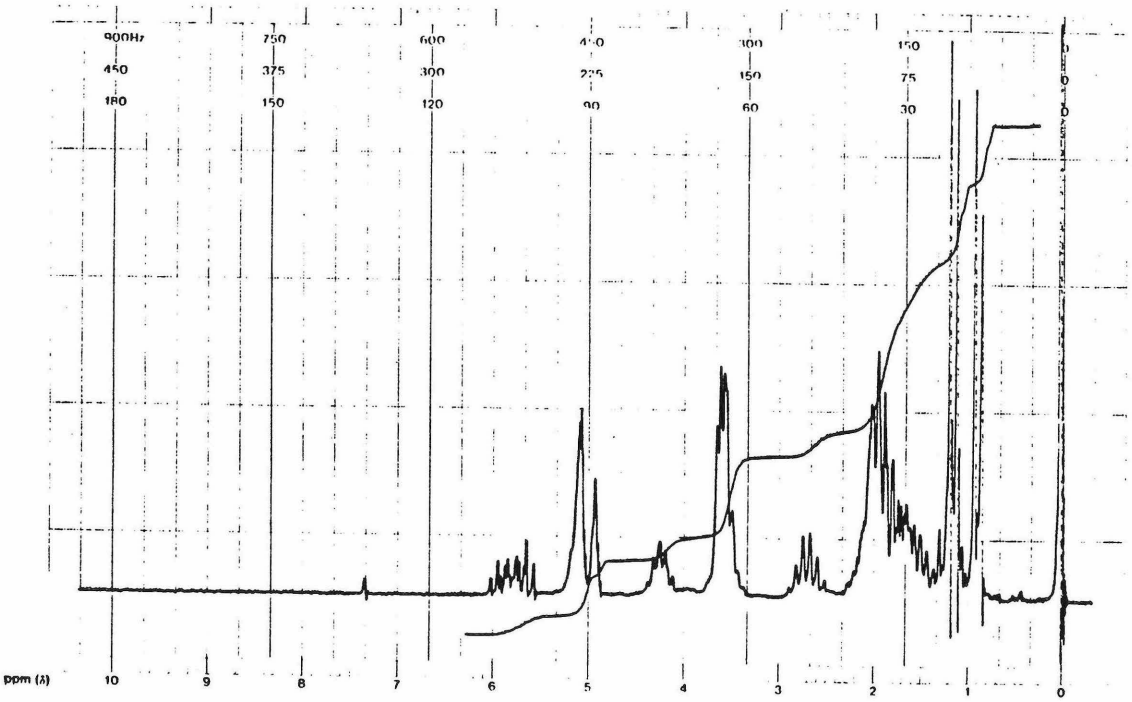


Neat

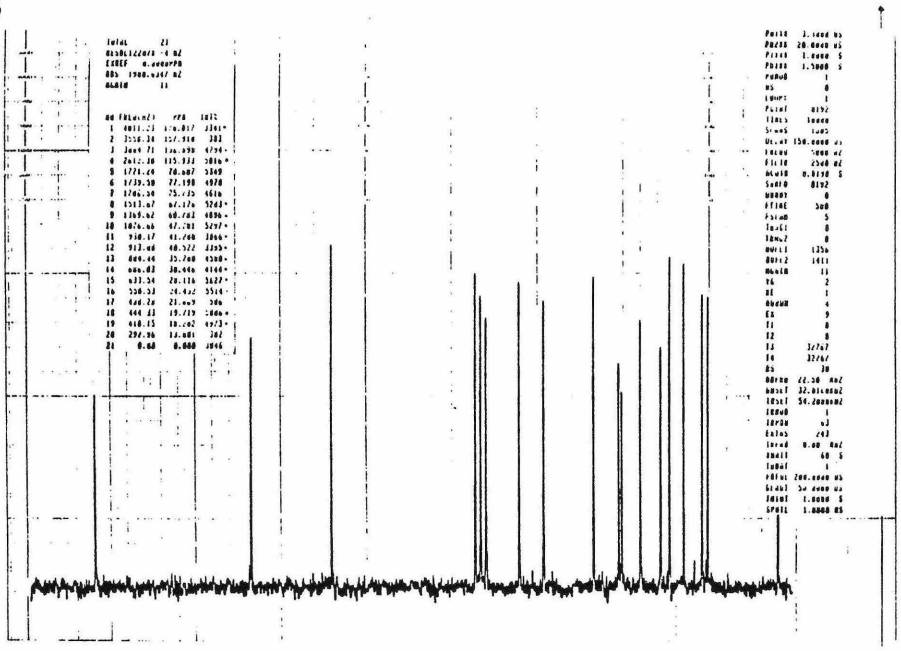
50



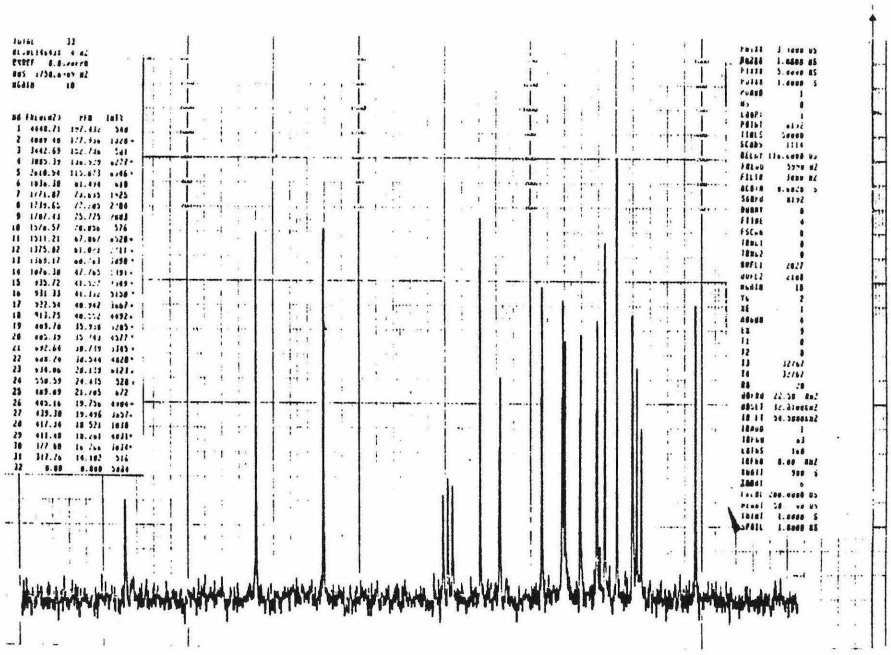
$CDCl_3$



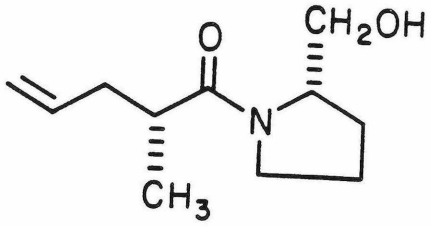
$CDCl_3$



$CDCl_3$ (authentic mixture)

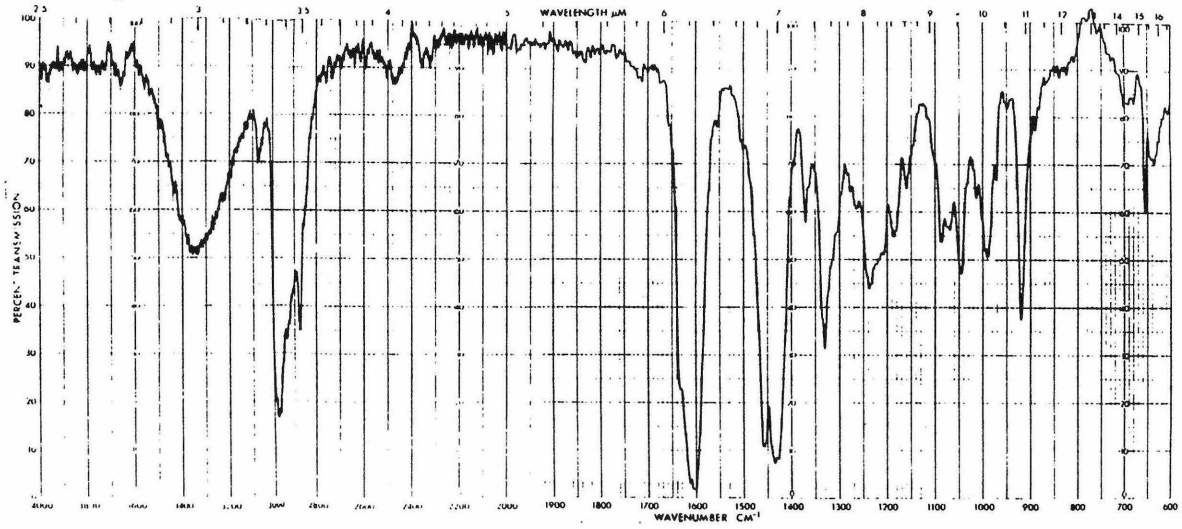


Page 101

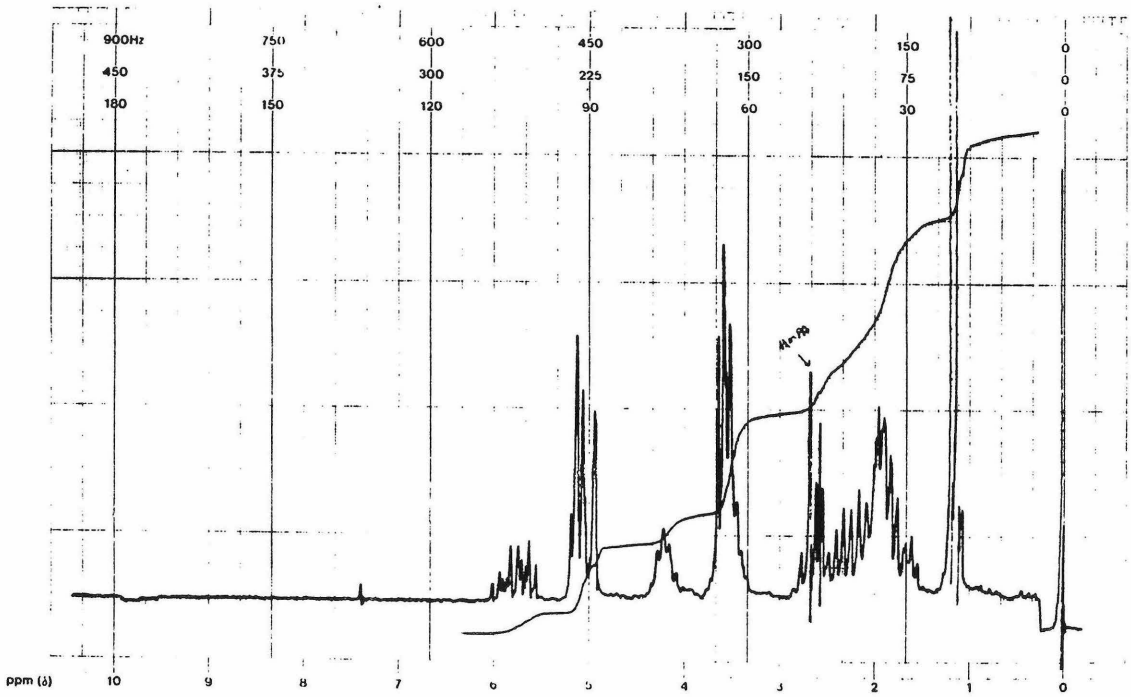


51

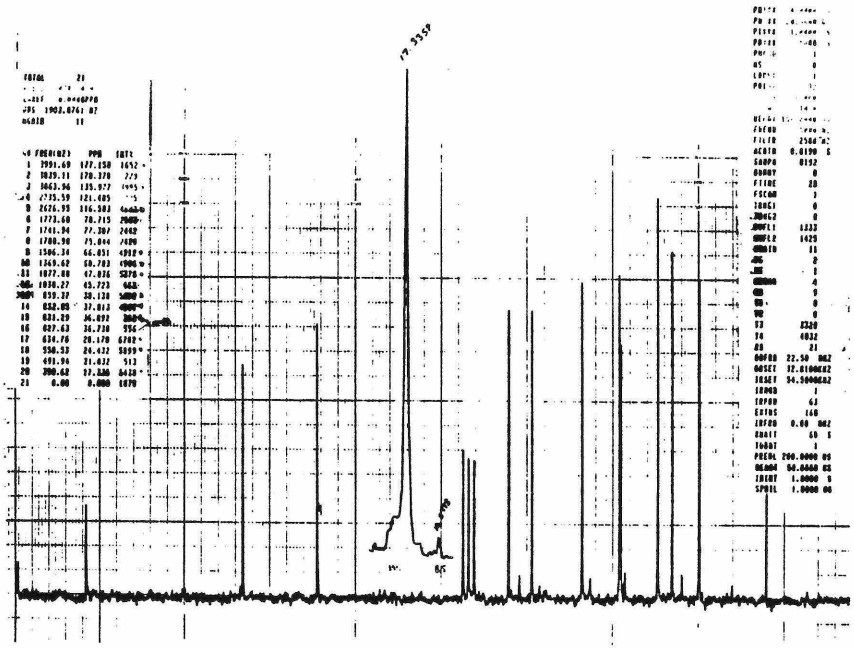
$CHCl_3$



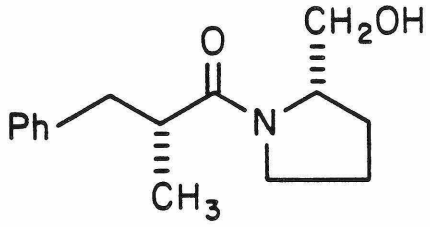
$CDCl_3$



$CDCl_3$

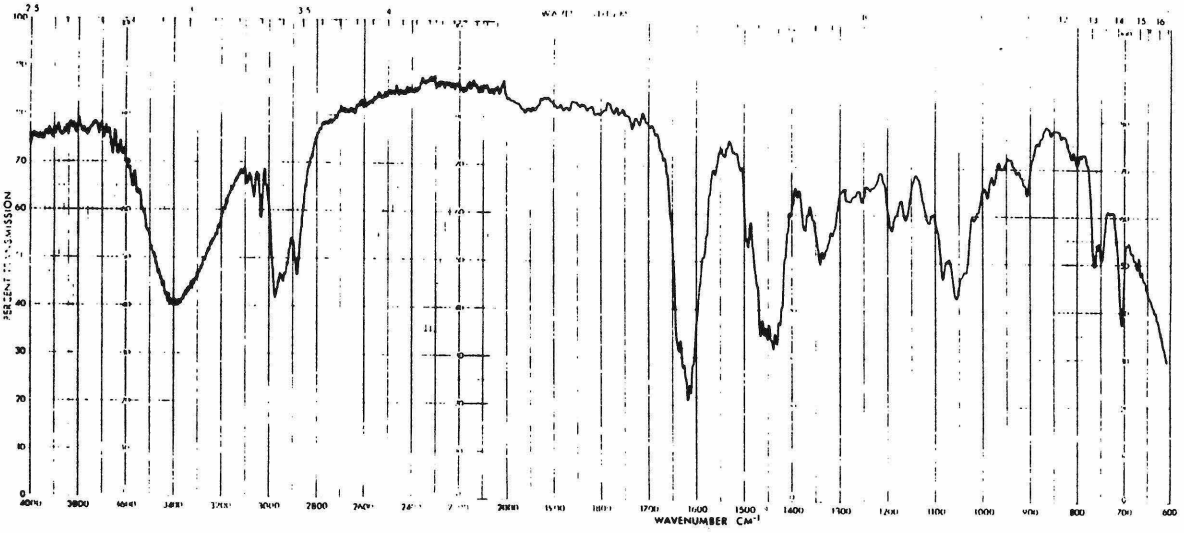


Page 102

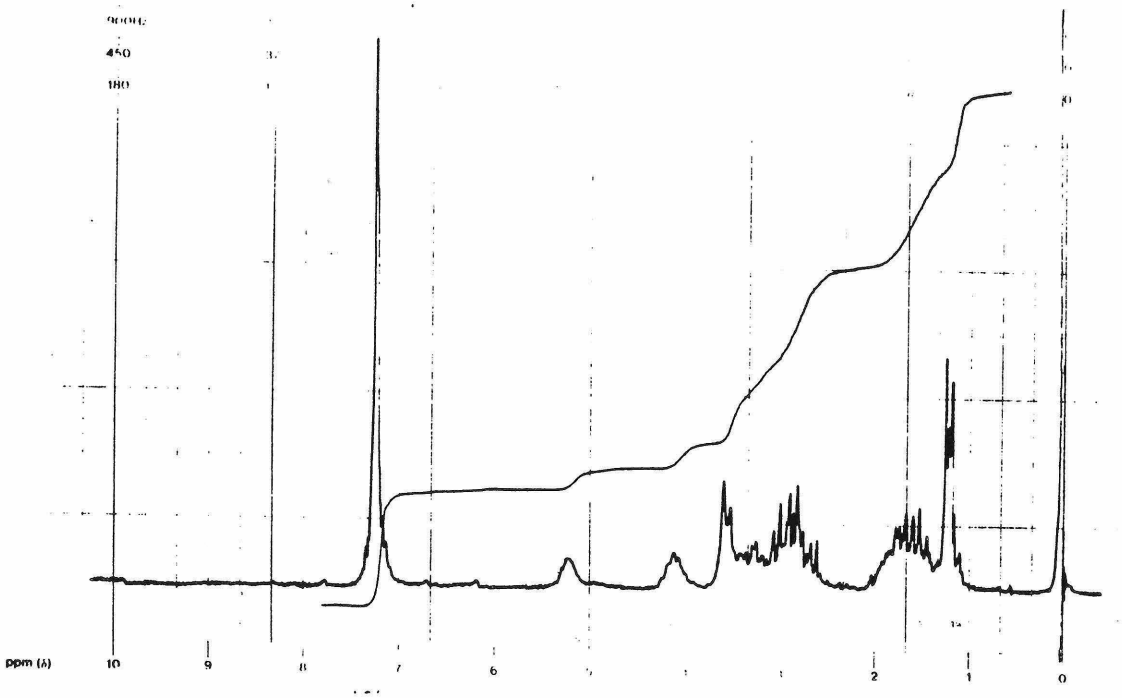


Neat

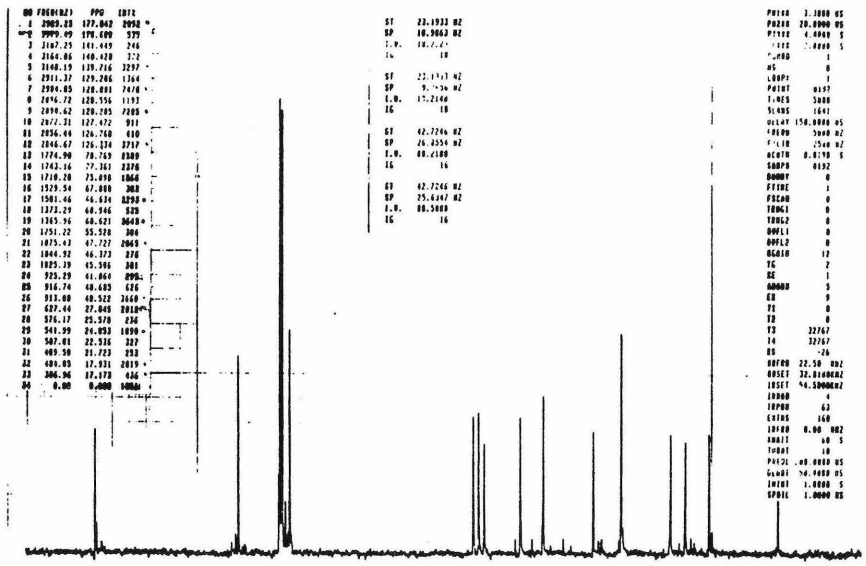
52



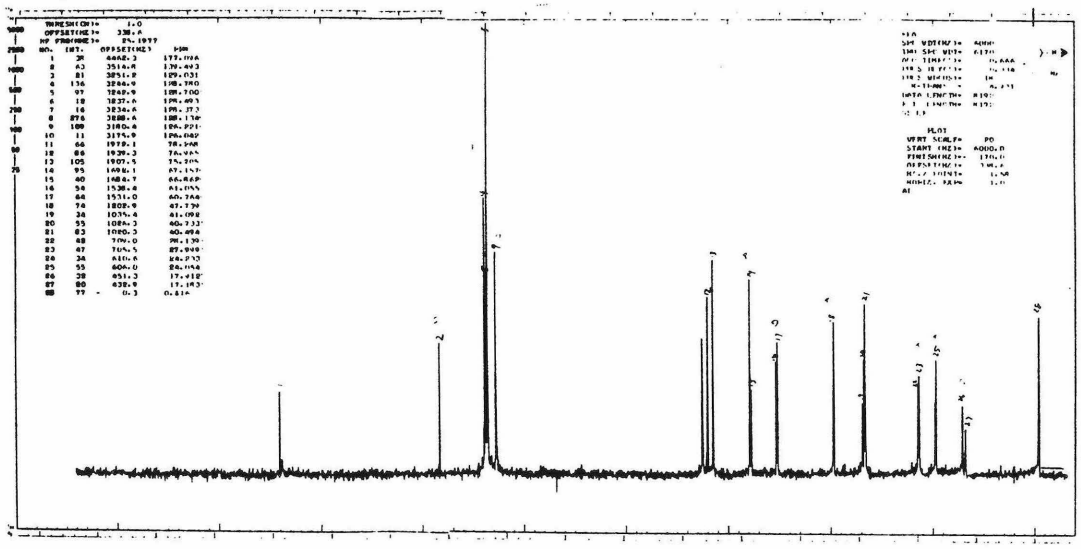
$CDCl_3$



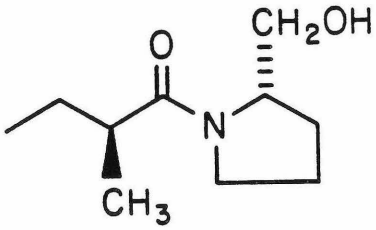
$CDCl_3$



$CDCl_3$ (authentic mixture)

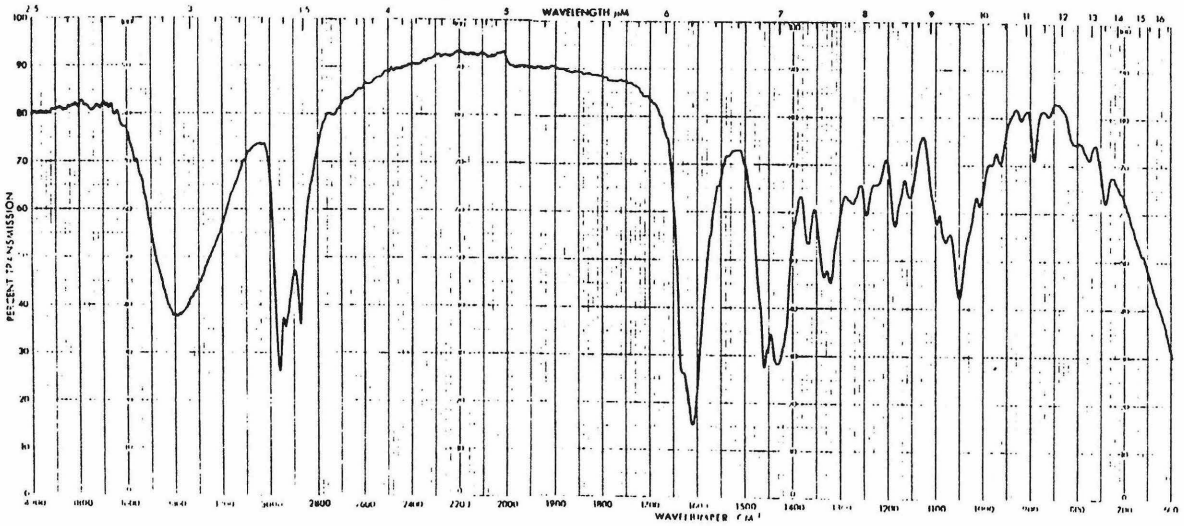


Page 104

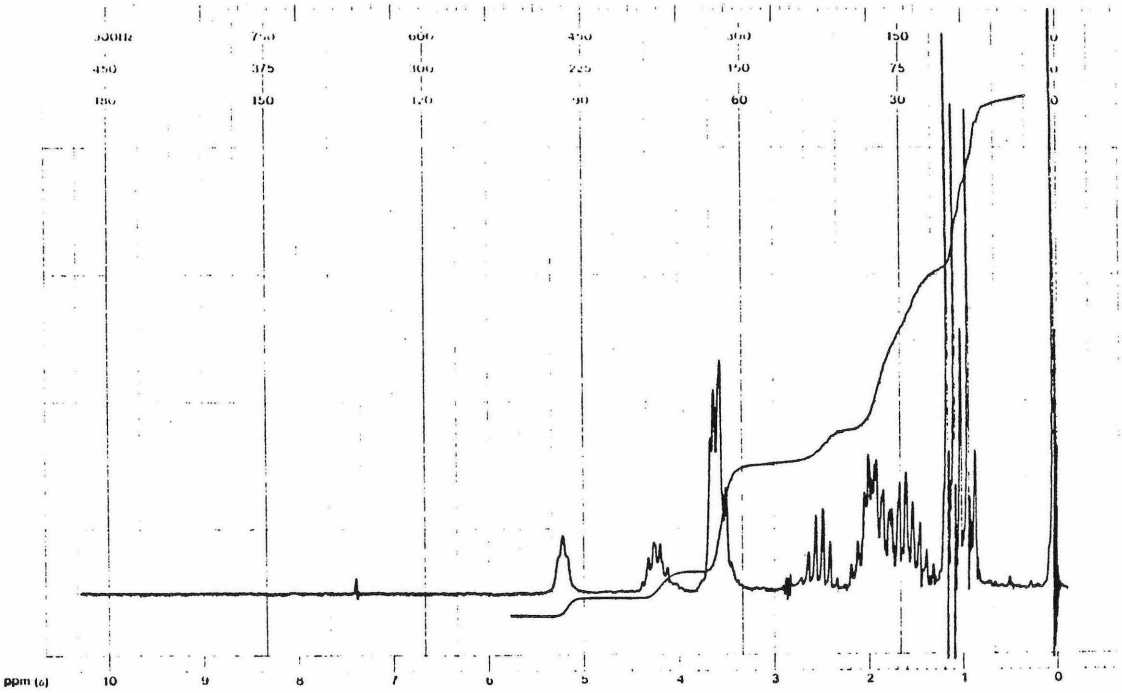


Neat

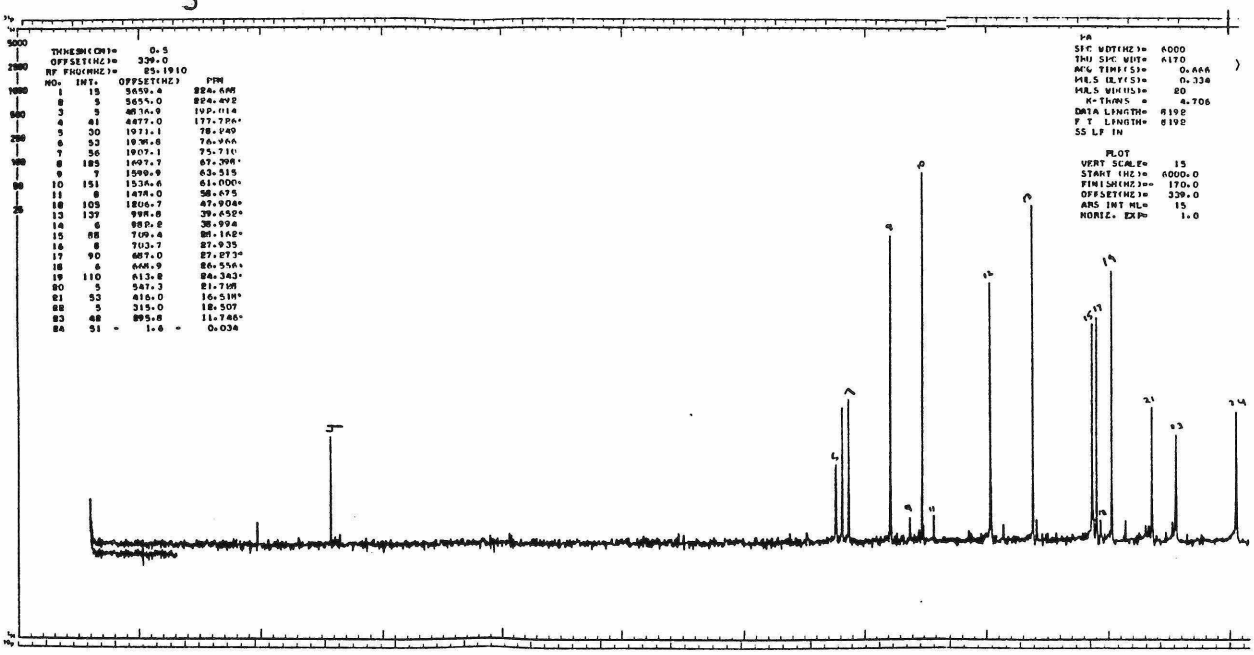
29



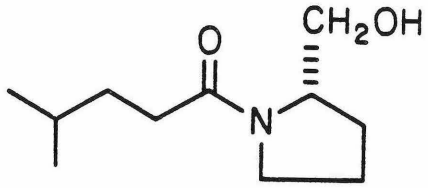
$CDCl_3$



$CDCl_3$

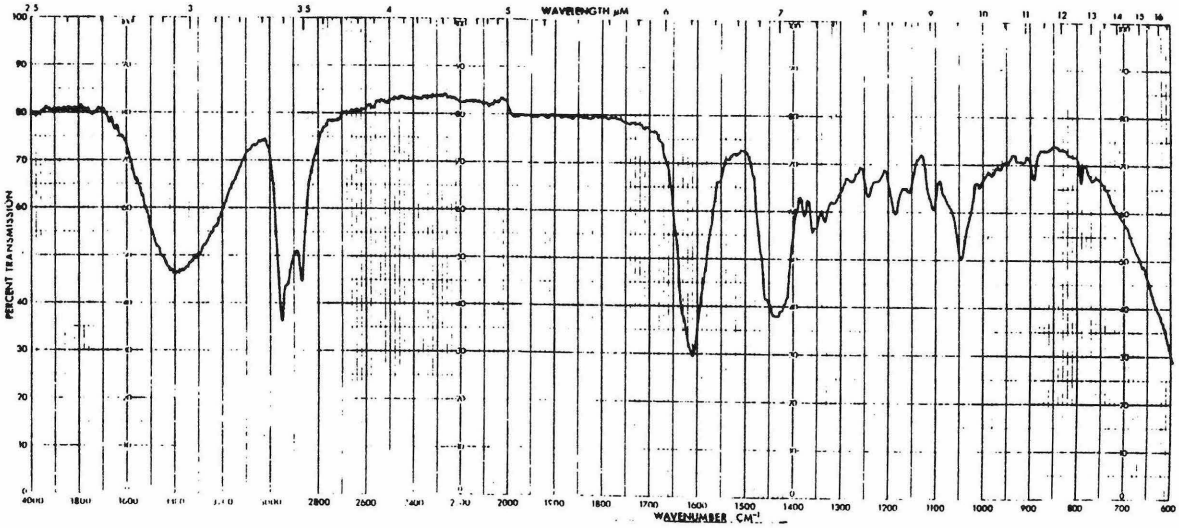

THRESH(CM)= 0.5
OFFSET(HZ)= 339.0
RF FRQ(MHZ)= 85.1910
NO. INT. OFFSET(HZ) PPM
1 15 5659.4 224.6MM
2 5 5654.0 224.492
3 5 4874.9 192.114
4 41 4477.0 177.786
5 30 1971.1 78.949
6 53 1938.8 76.966
7 56 1907.1 75.710
8 185 1697.7 67.398
9 7 1599.9 63.515
10 151 1534.6 61.000
11 8 1478.0 58.675
12 105 1206.7 47.904
13 137 998.8 39.652
14 6 989.2 38.994
15 88 709.4 28.162
16 8 703.7 27.935
17 90 687.0 27.273
18 6 668.9 26.558
19 110 613.8 24.363
20 5 547.3 21.718
21 53 416.0 16.518
22 5 315.0 12.507
23 48 295.8 11.746
24 51 1.6 0.034
FA
SPC WDT(HZ)= 4000
THU SPC WDT= 4170
AVG TIME(S)= 0.666
MRLS DLY(S)= 0.334
MRLS WDH(US)= 20
K-TRANS = 4.706
DATA LENGTH= 8192
F T LENGTH= 8192
SS LF IN
PLOT
VERT SCALE= 15
START (HZ)= 4000.0
FINISH(HZ)= 170.0
OFFSET(HZ)= 339.0
ARS INT ML= 15
HORIZ. EXP= 1.0

Page 105

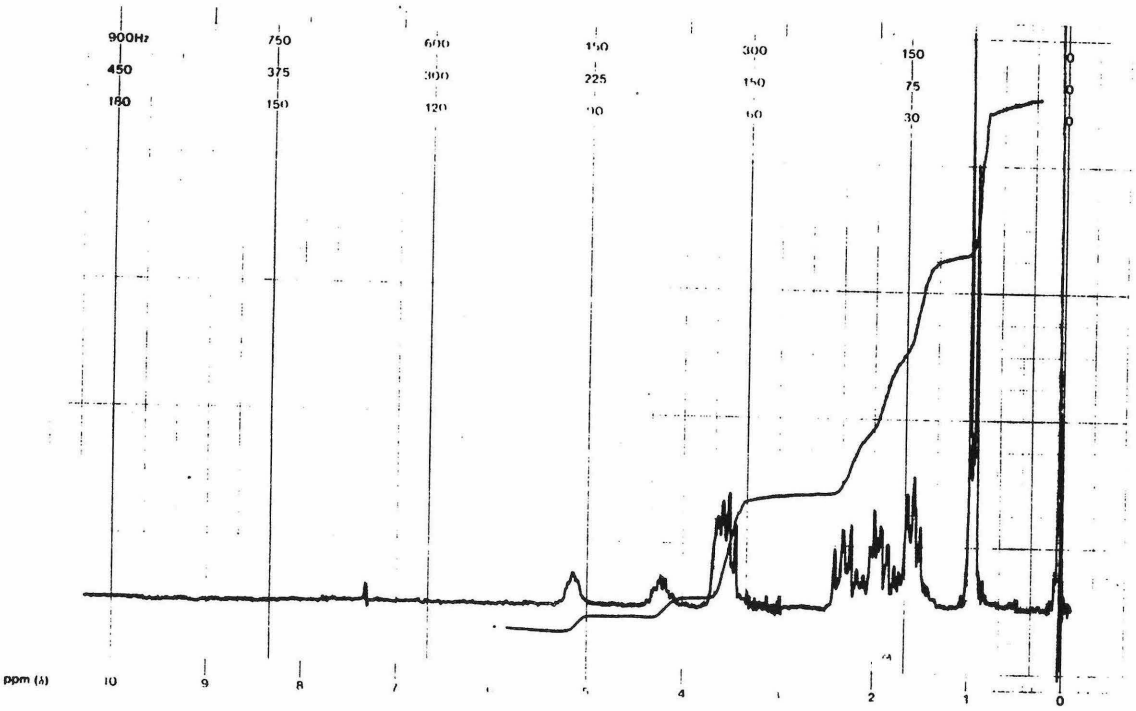


18

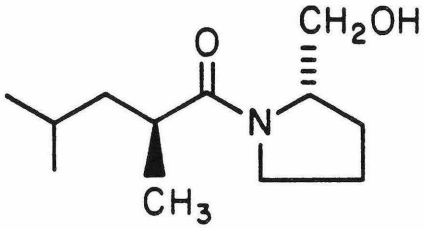
Neat



$CDCl_3$

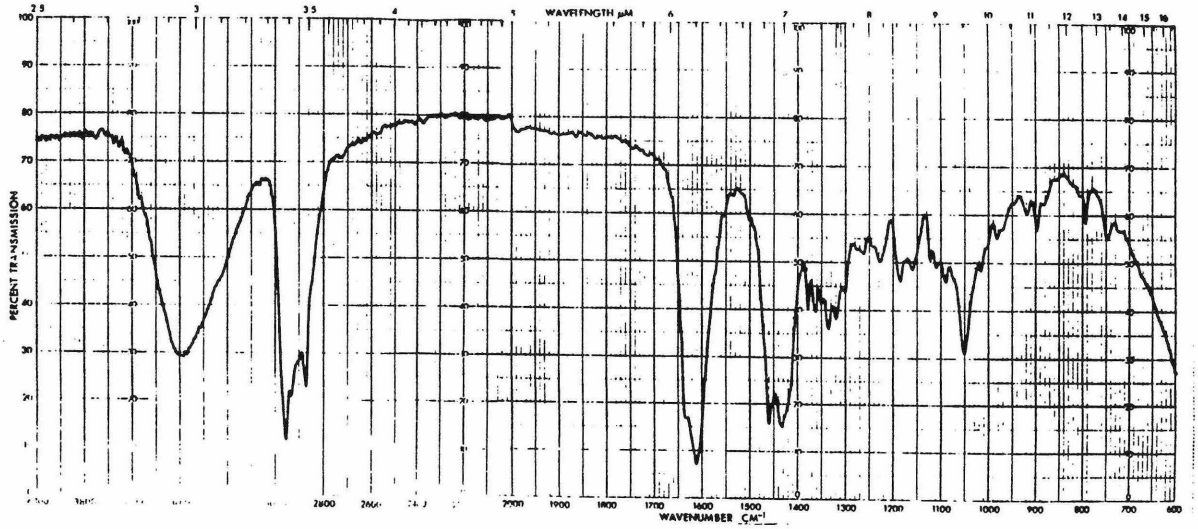


Page 106

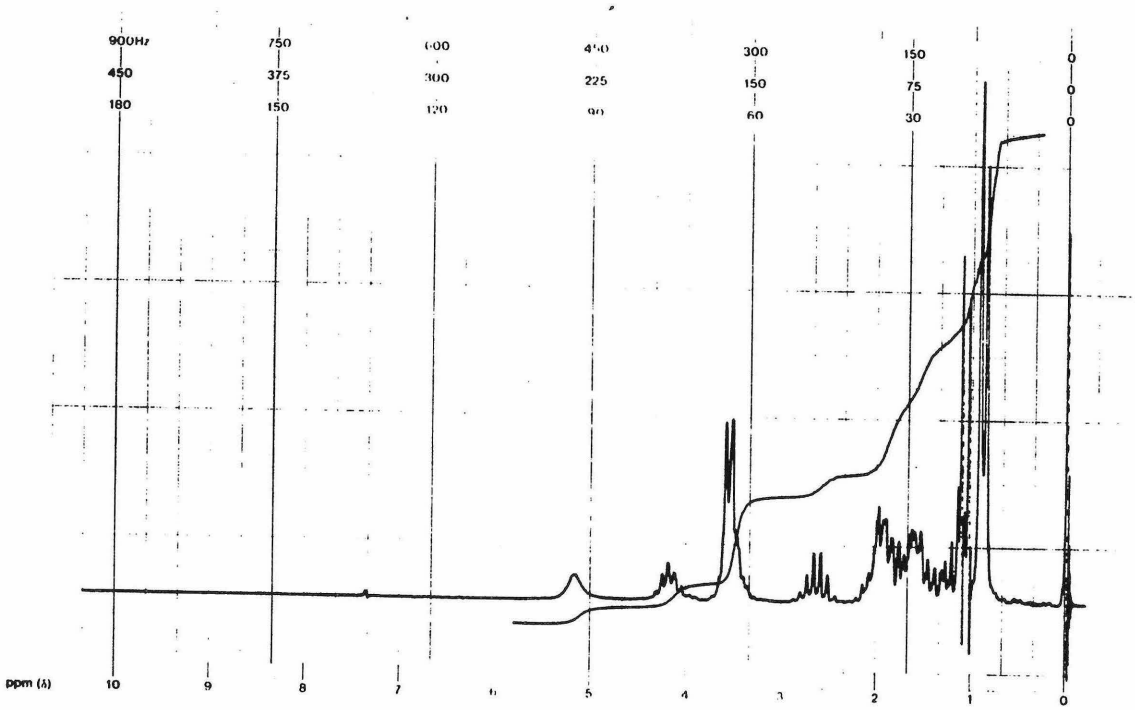


46

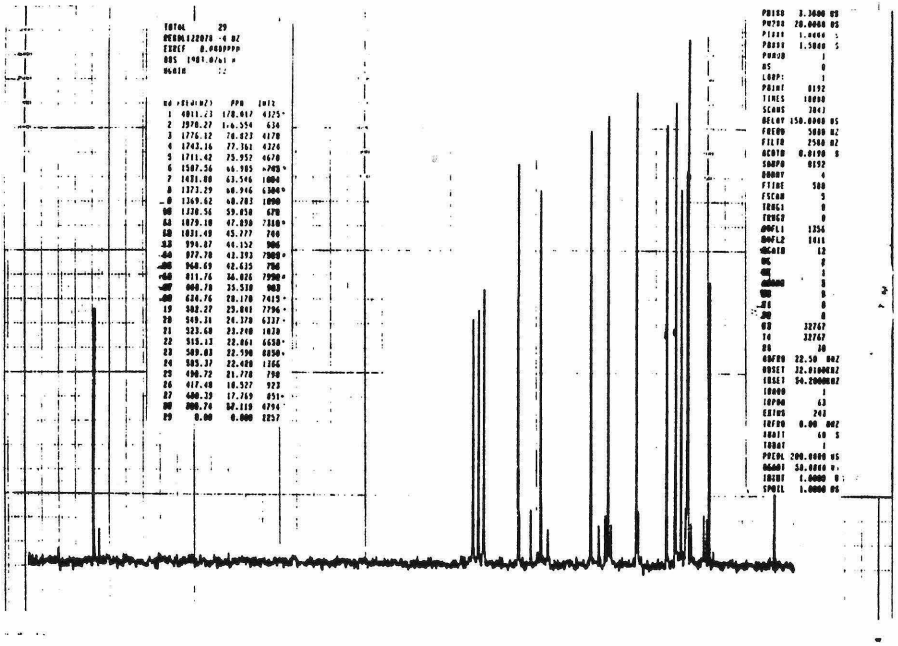
Neat



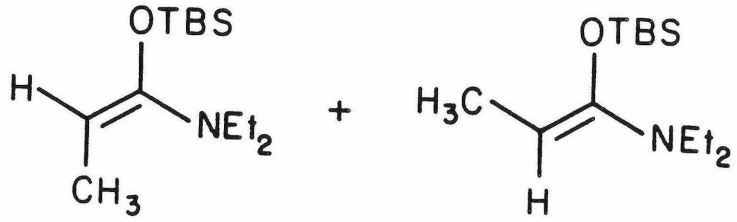
$CDCl_3$



$CDCl_3$

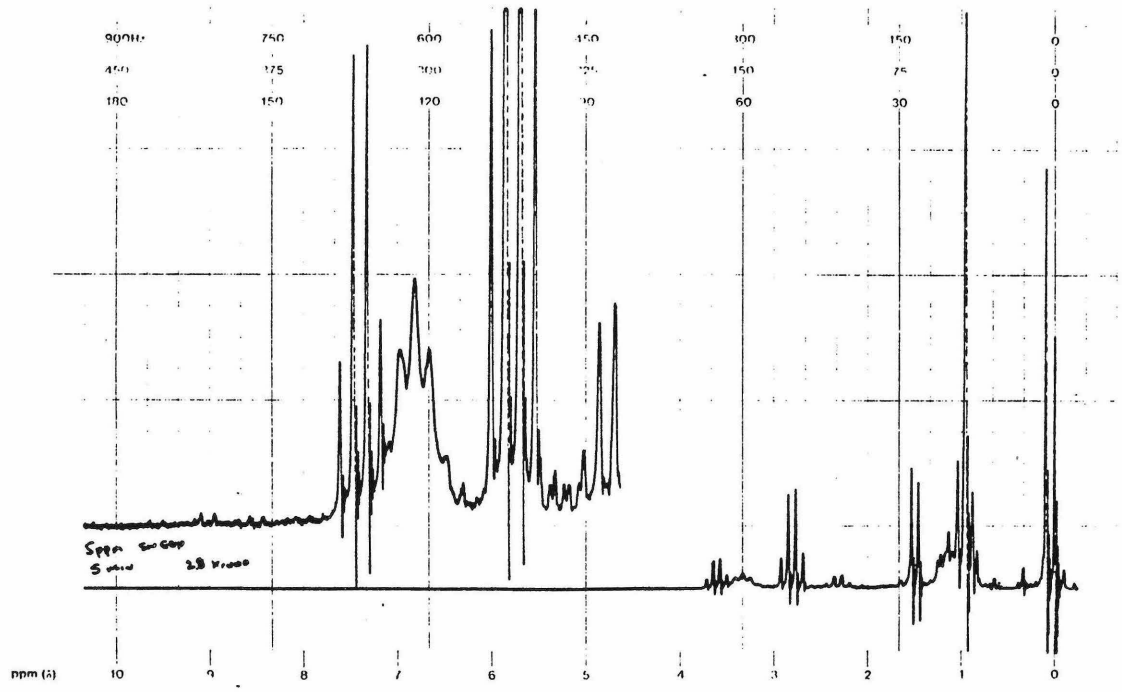


Page 107

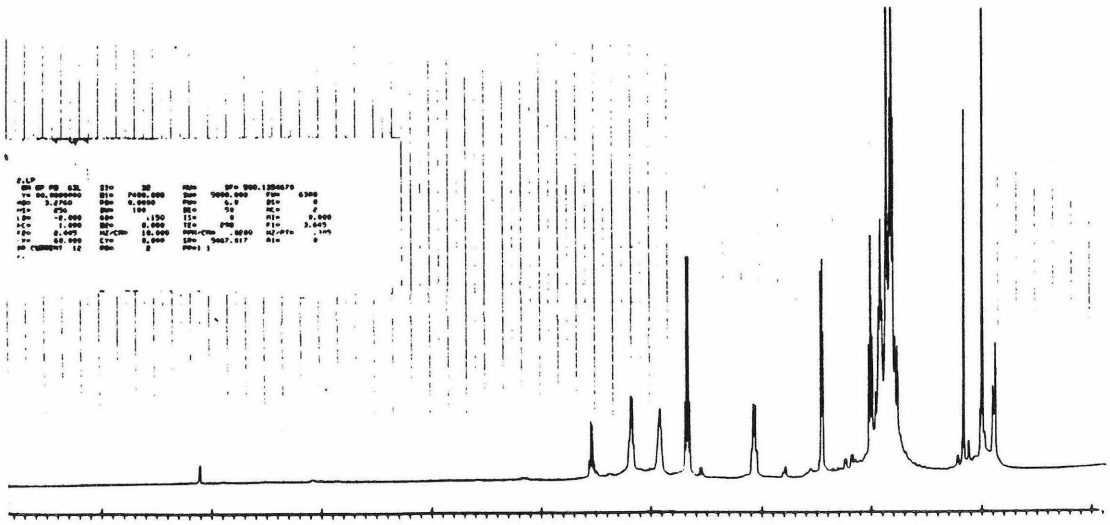


2 3

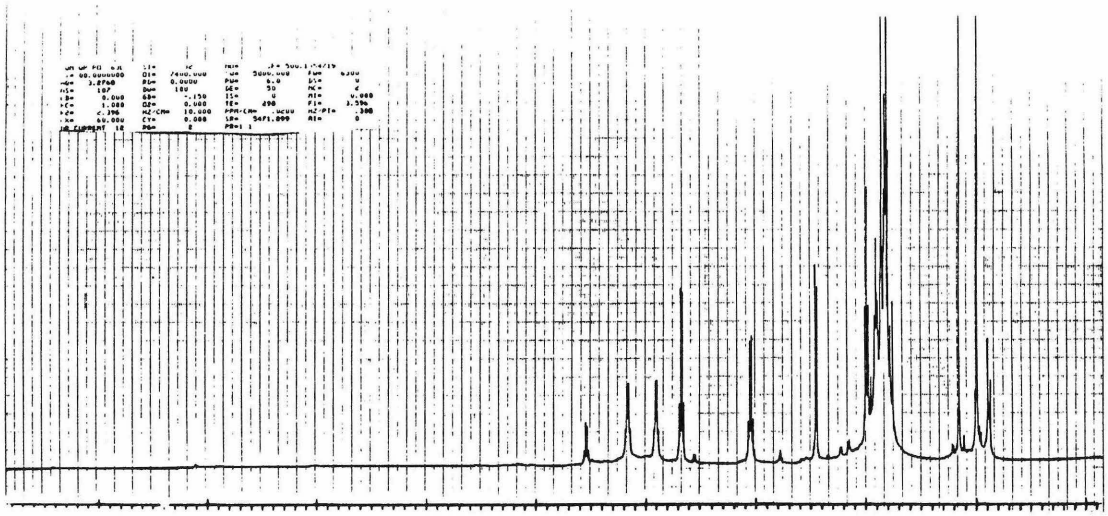
CCl_4 (90 MHz ^1H NMR)



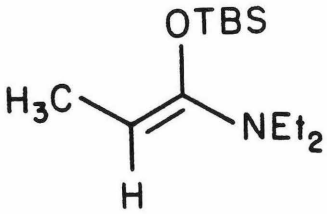
CCl_4 (500 MHz ^1H NMR)



CCl_4 (500 MHz ^1H NMR-isomerized product)

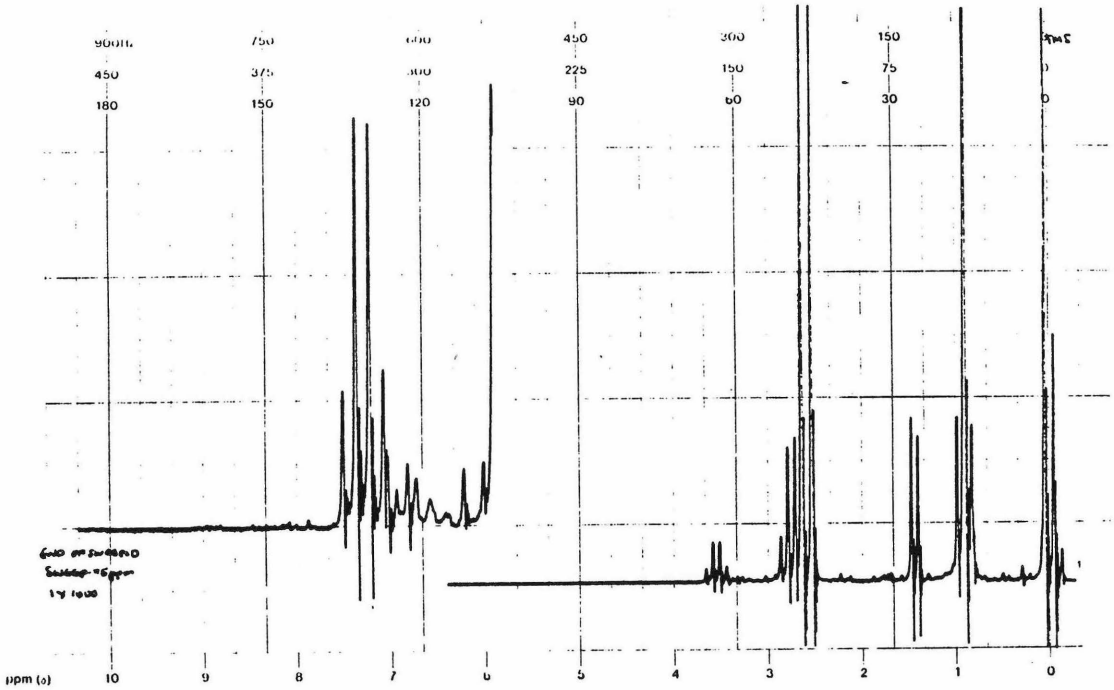


Page 107

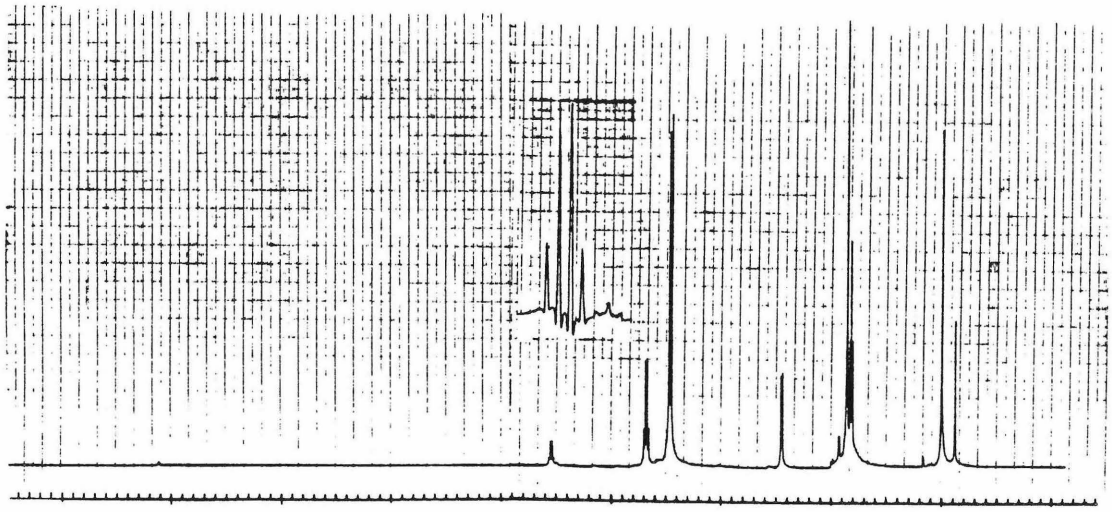


3

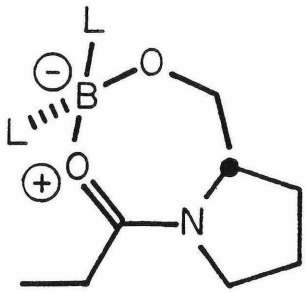
CCl_4 (90 MHz ^1H NMR)



CCl_4 (500 MHz ^1H NMR)

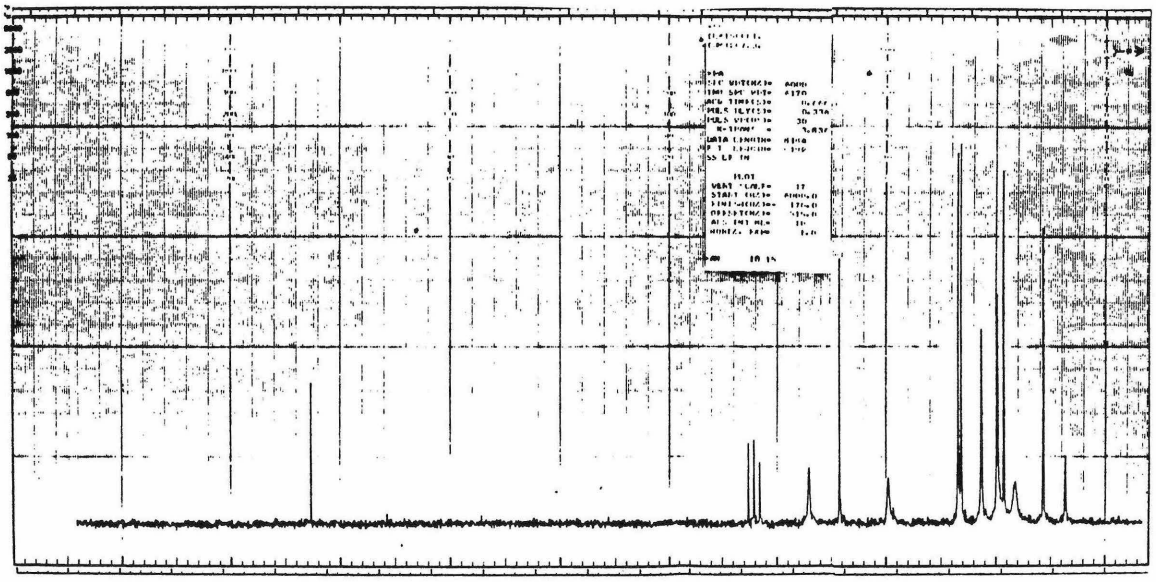


Page 108

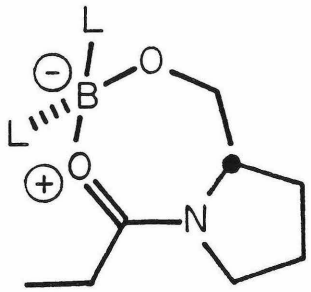


22, L = n-C_6H_{13}

$CDCl_3$

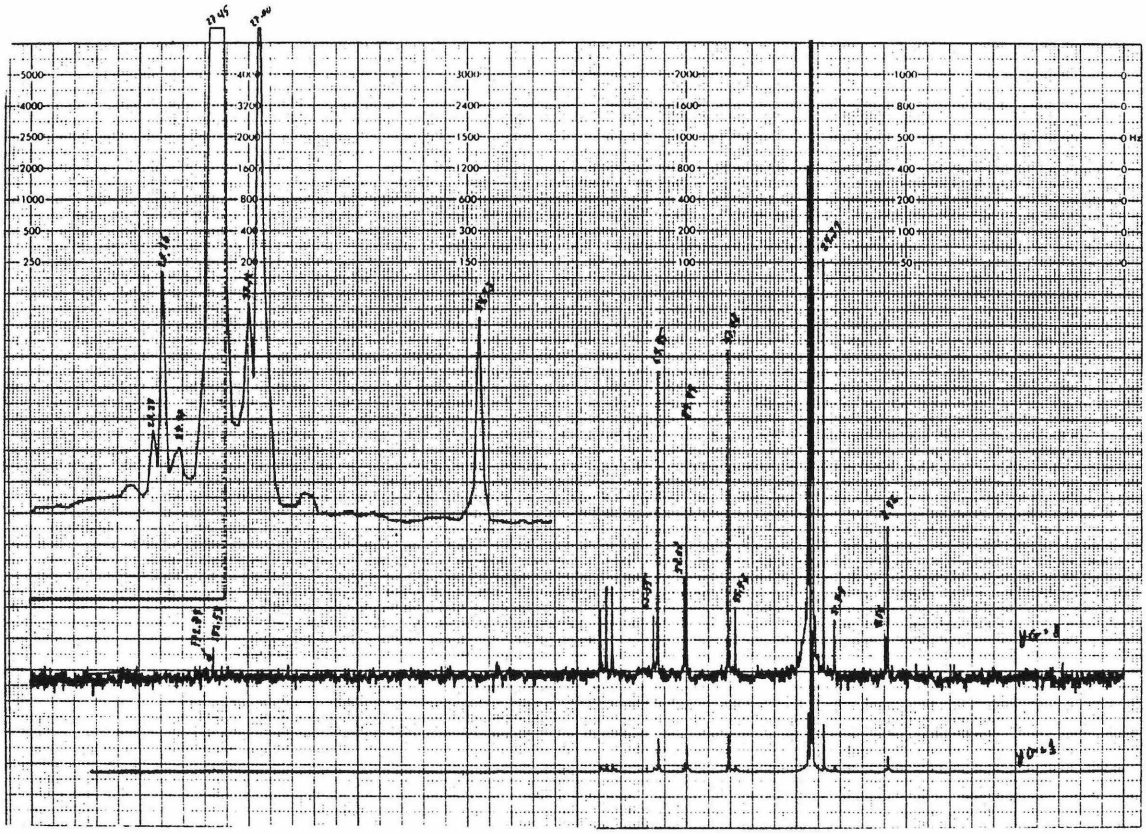


Page 109

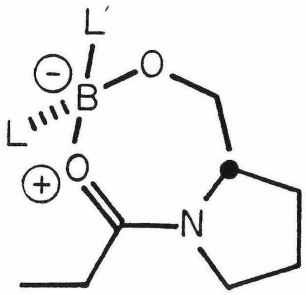


24, L = C_6H_{11}

$CDCl_3$

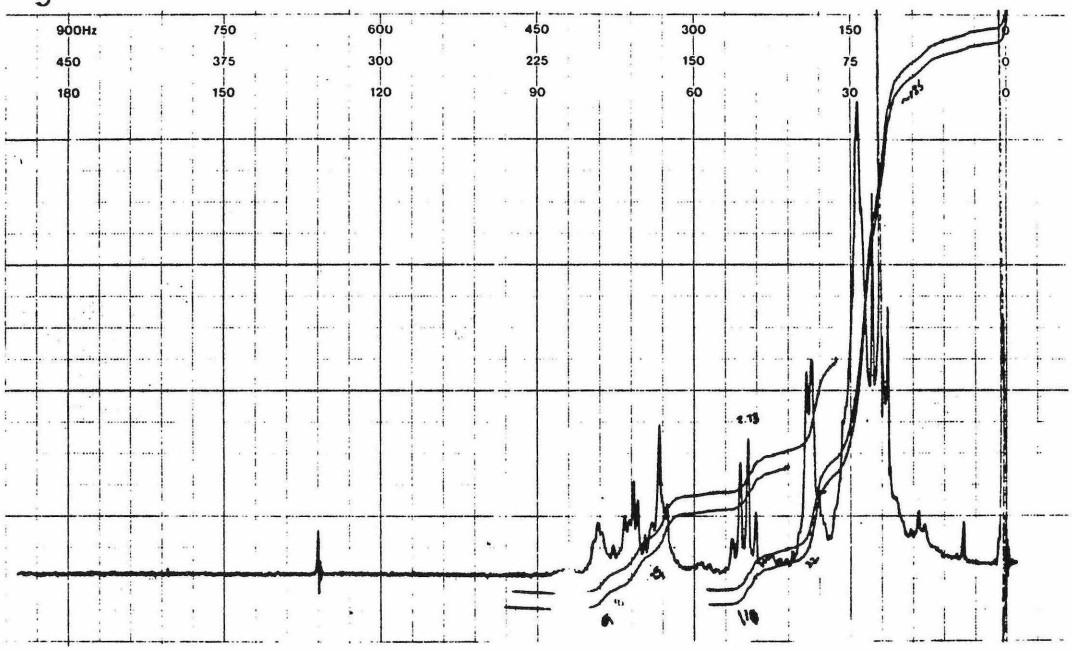


Page 109

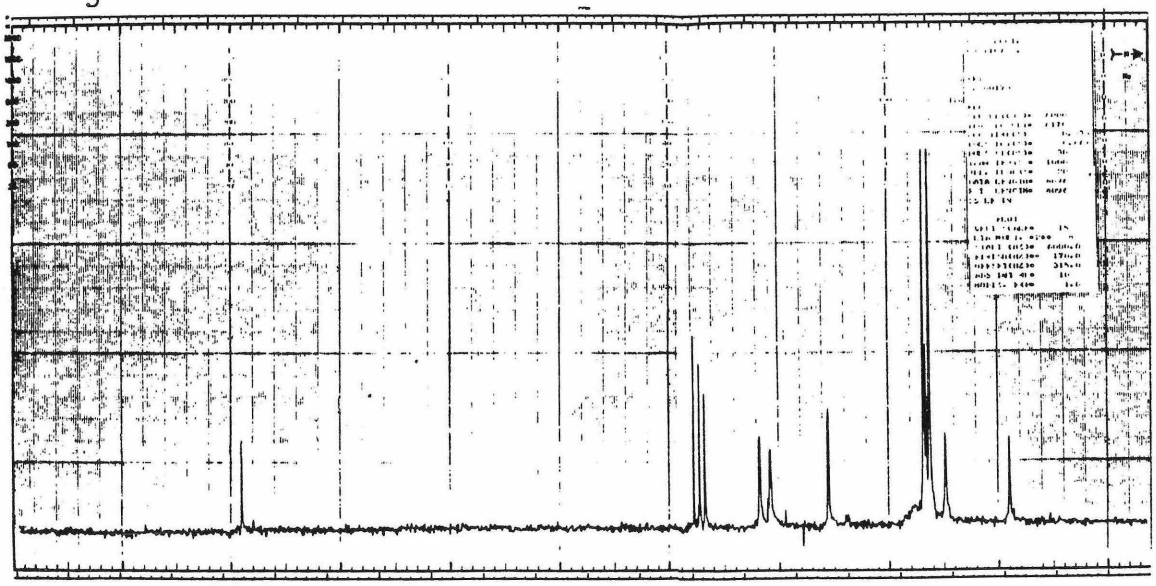


25, L = C_5H_9

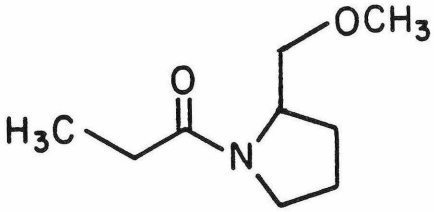
$CDCl_3$



$CDCl_3$

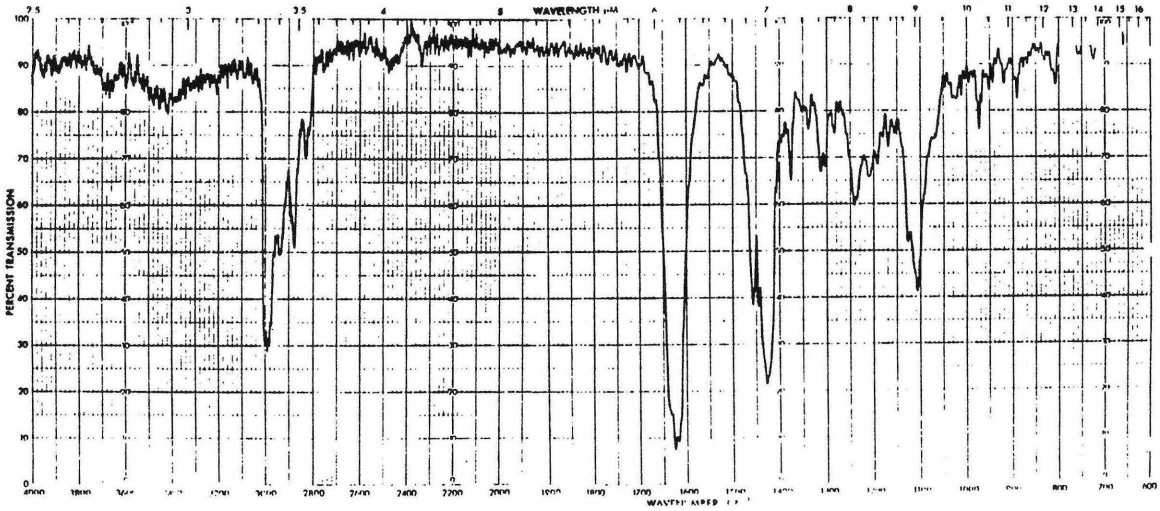


Page 111

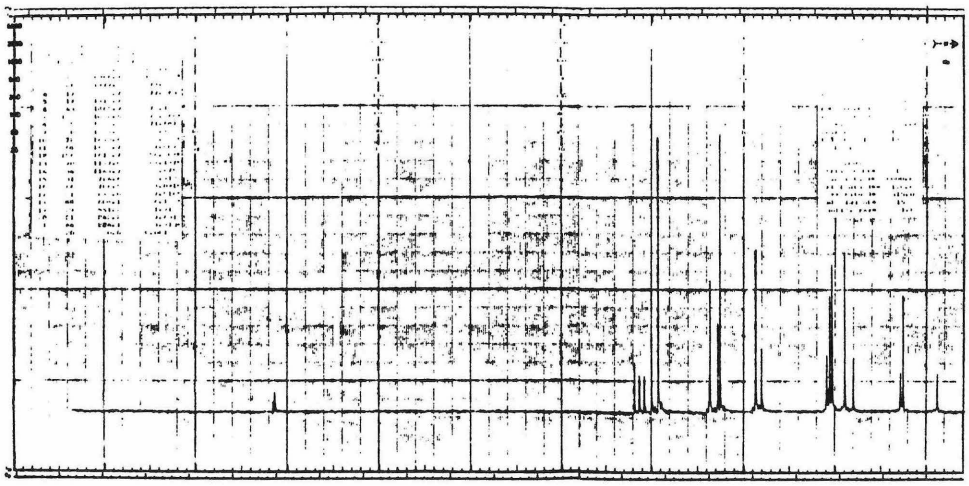


30

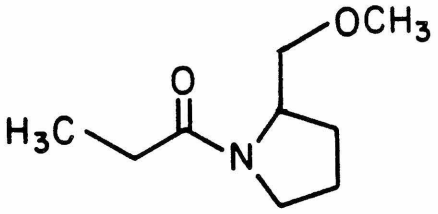
$CHCl_3$



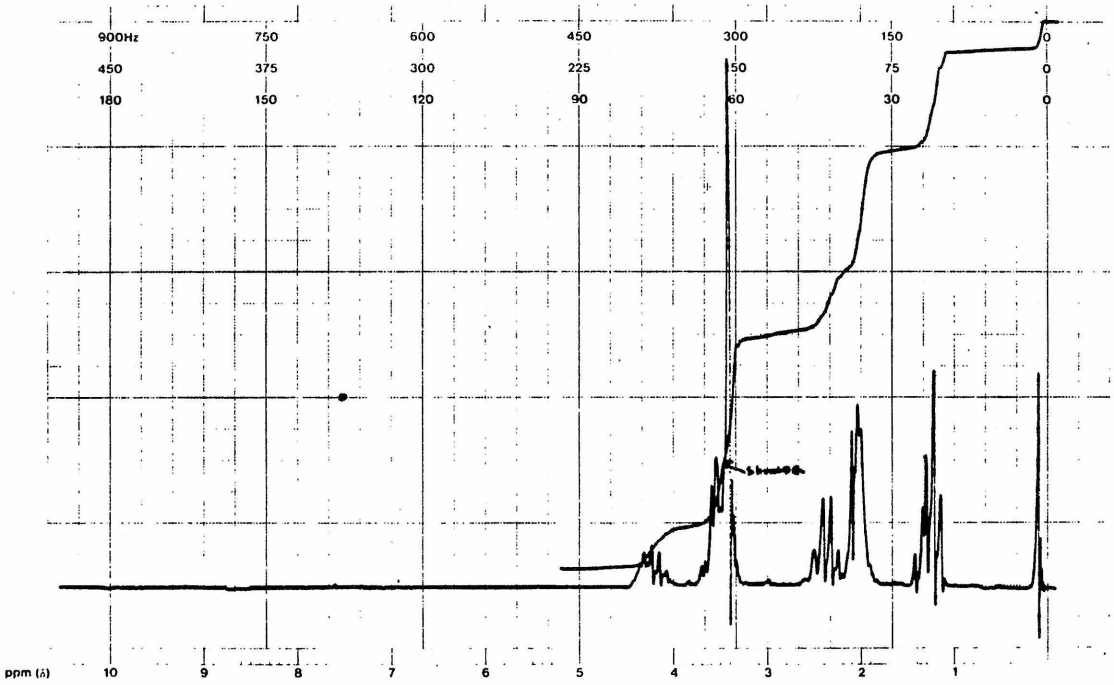
$CDCl_3$



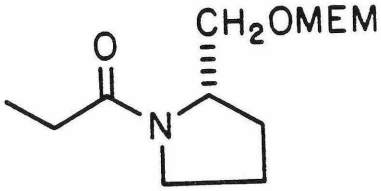
Page 111



$CDCl_3$

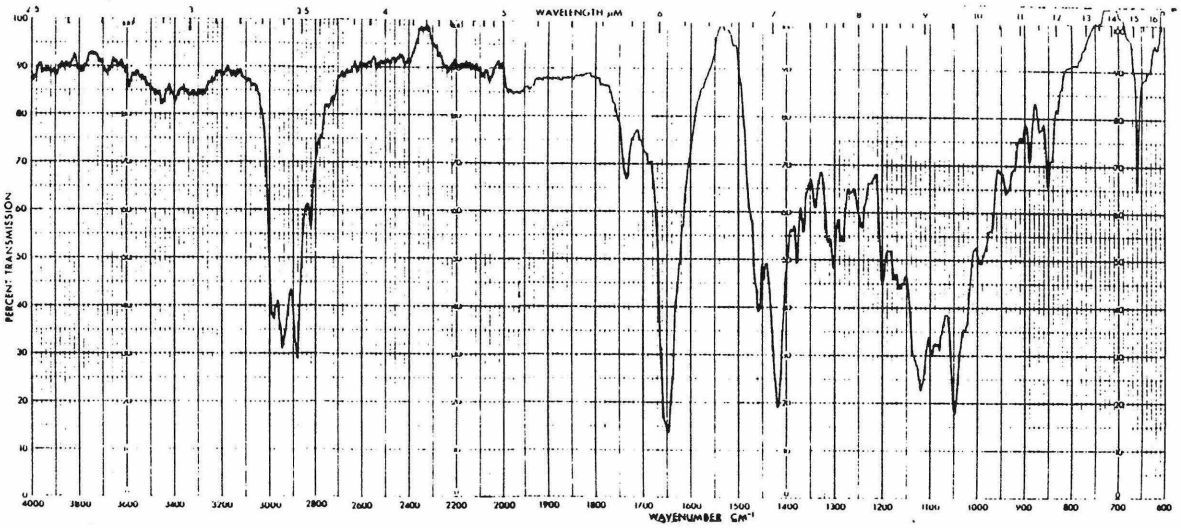


Page 112

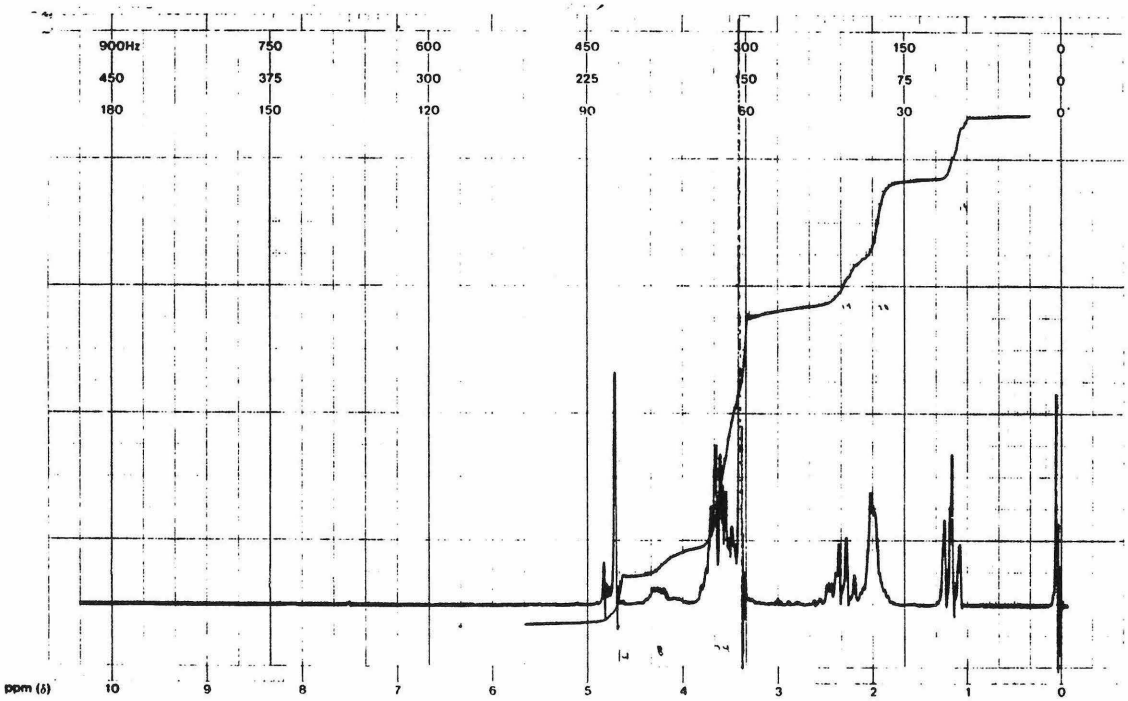


32

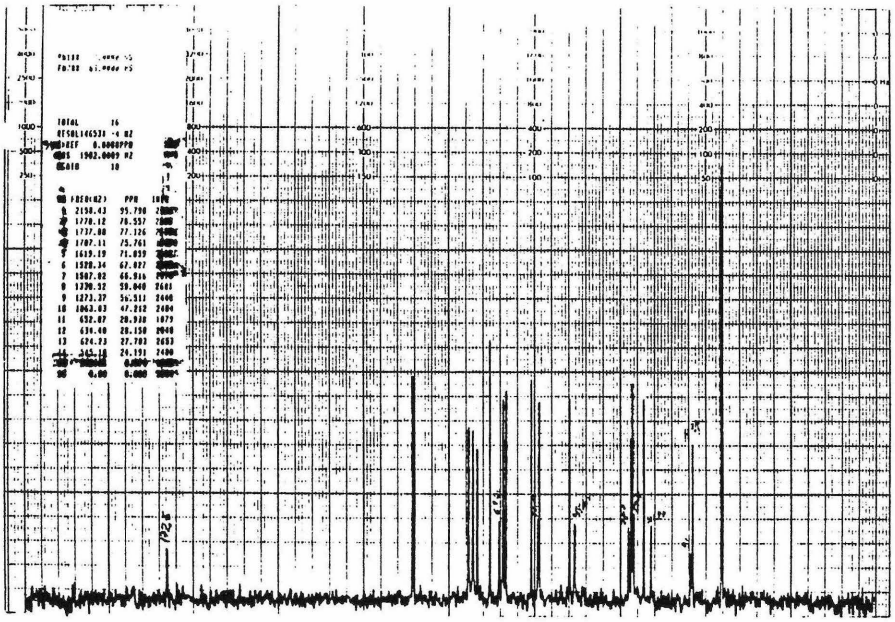
CCl_4



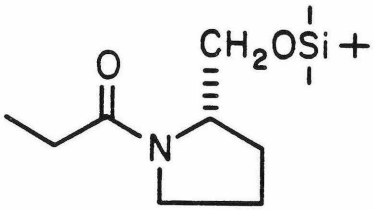
$CDCl_3$



$CDCl_3$

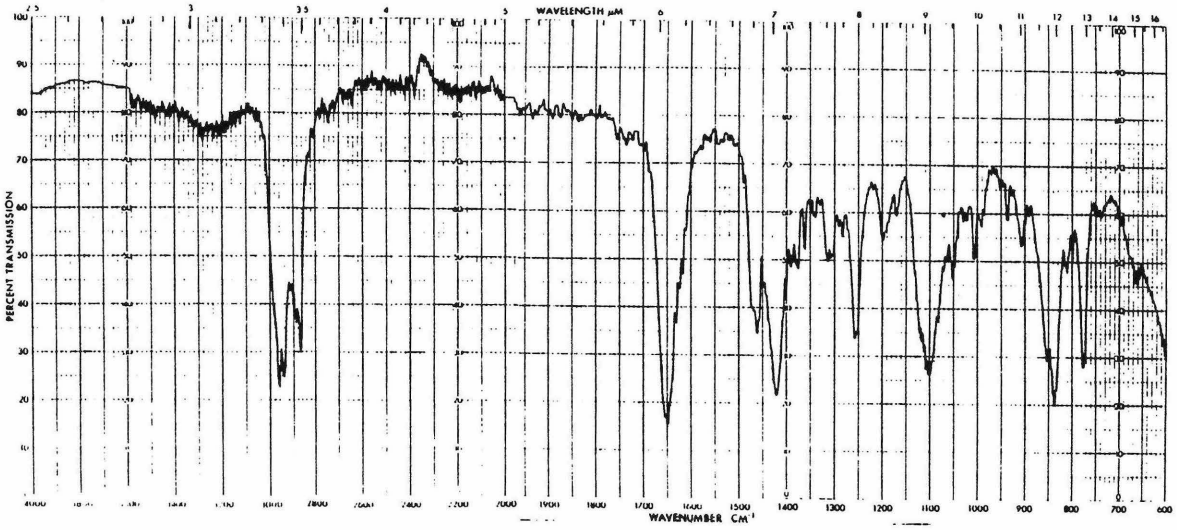


Page 113

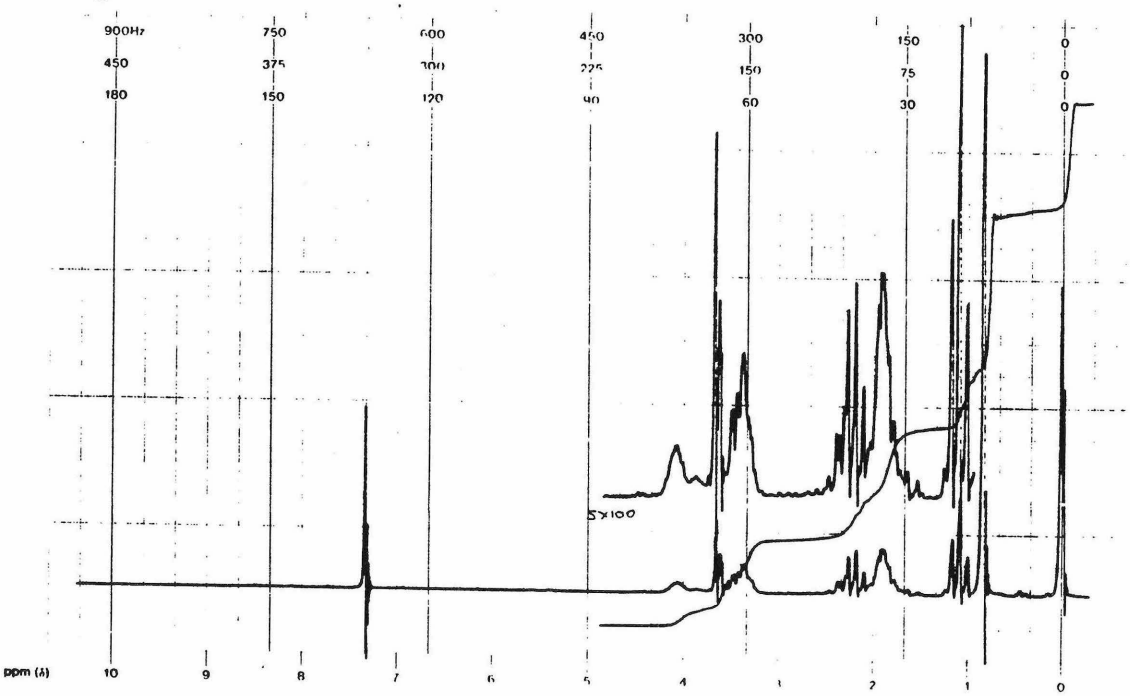


33

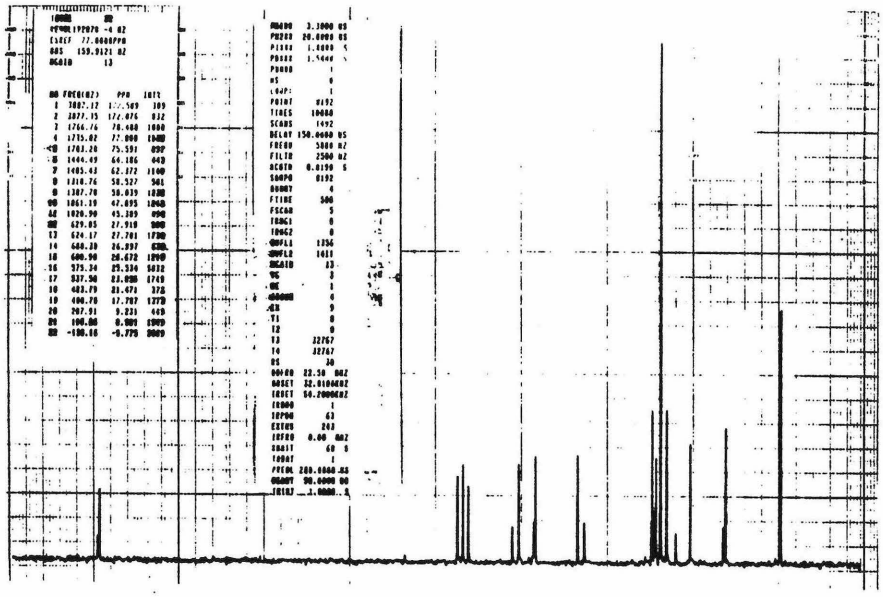
Neat



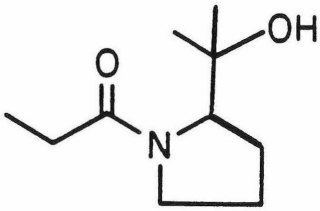
$CDCl_3$



$CDCl_3$

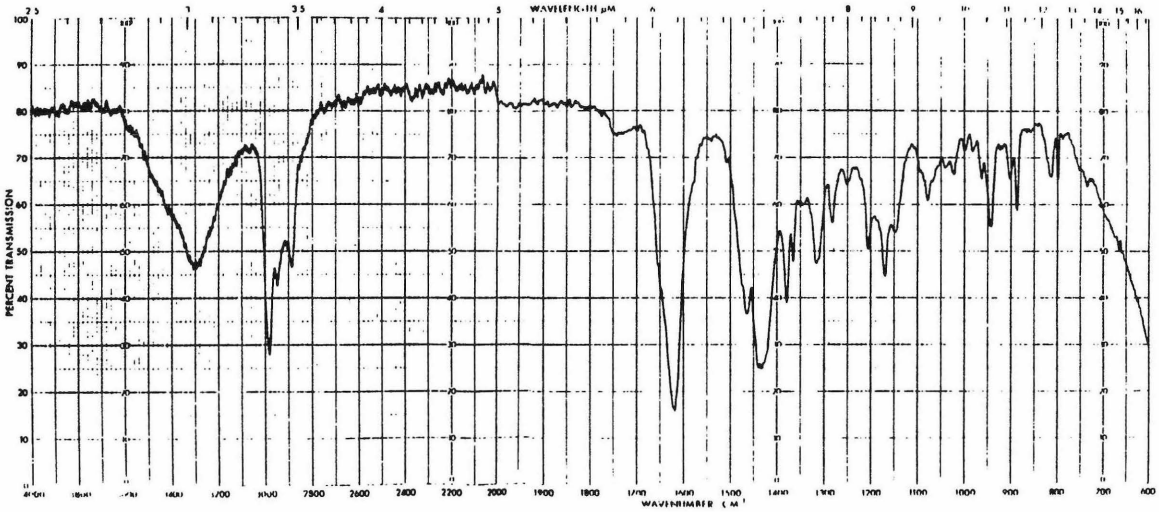


Page 113

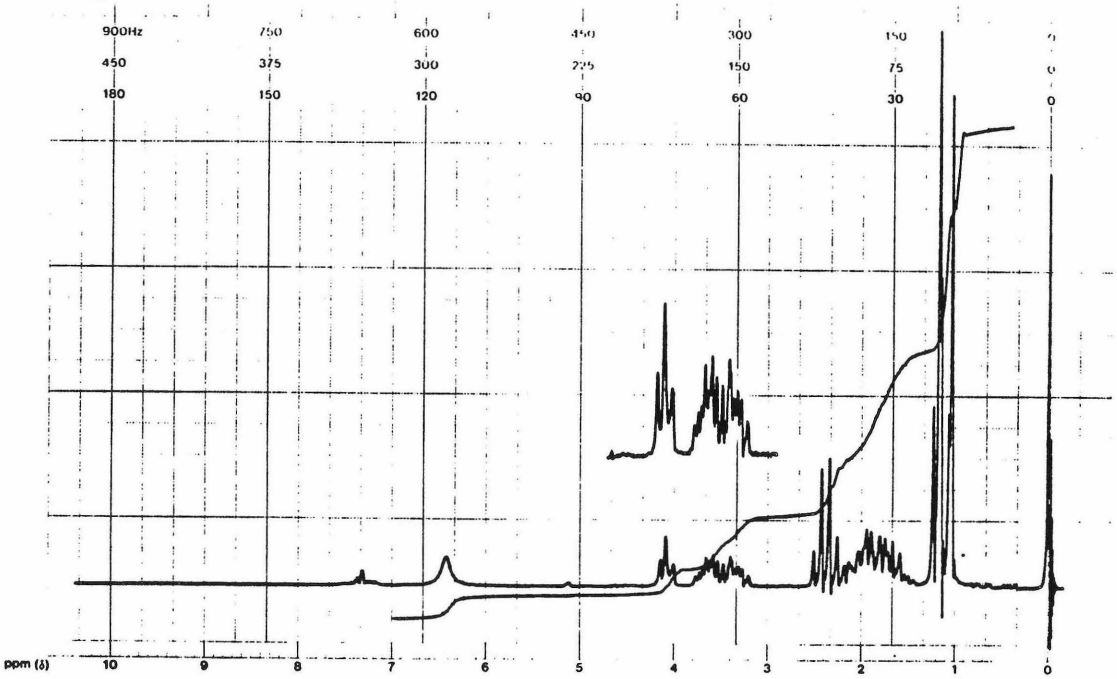


36

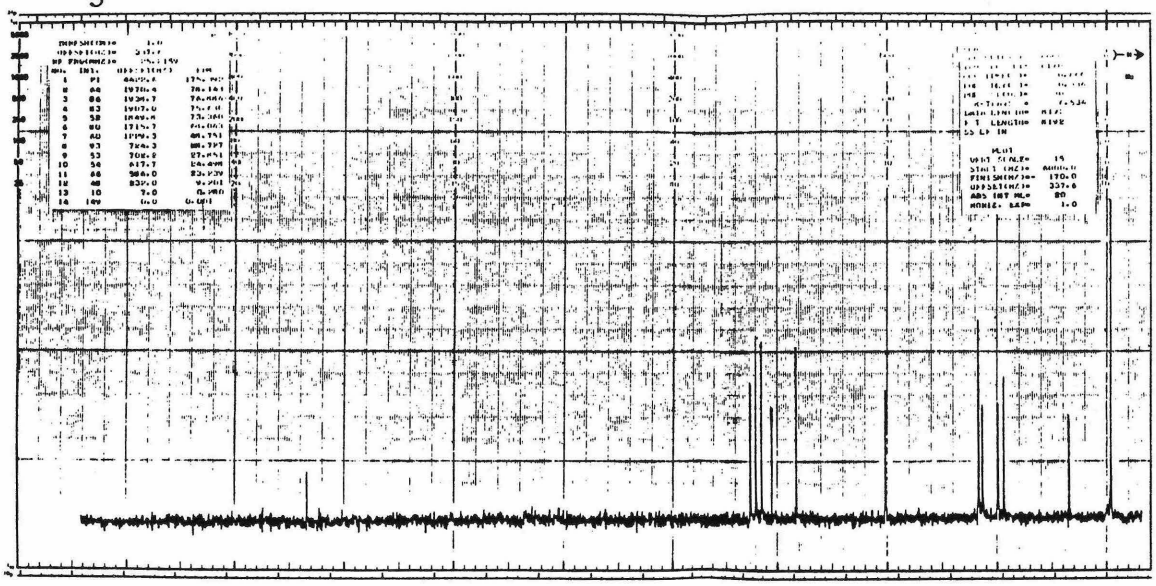
Neat



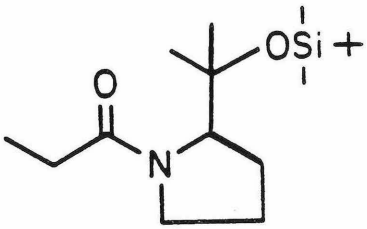
$CDCl_3$



CDC1 3

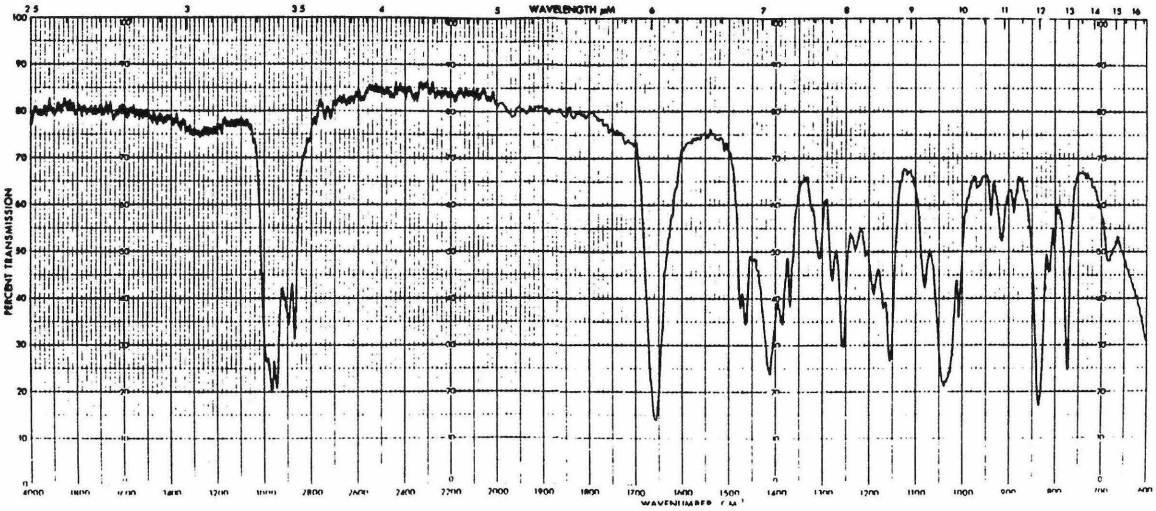


Page 114

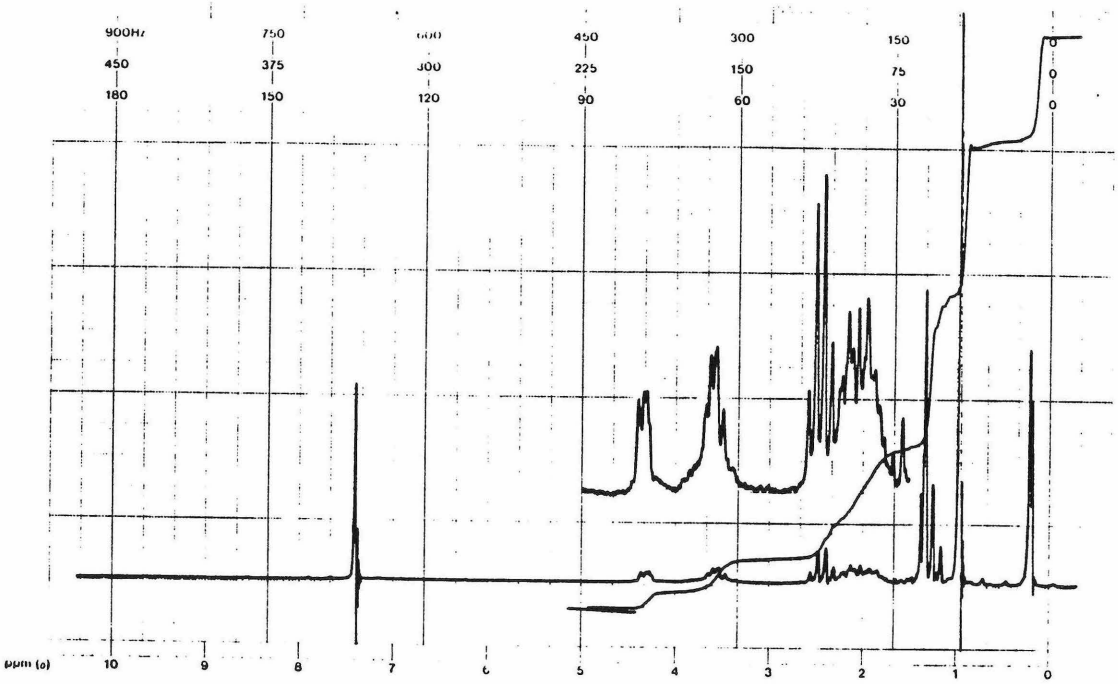


37

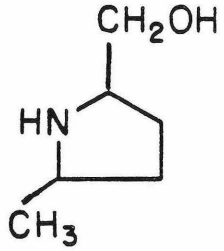
Neat



$CDCl_3$

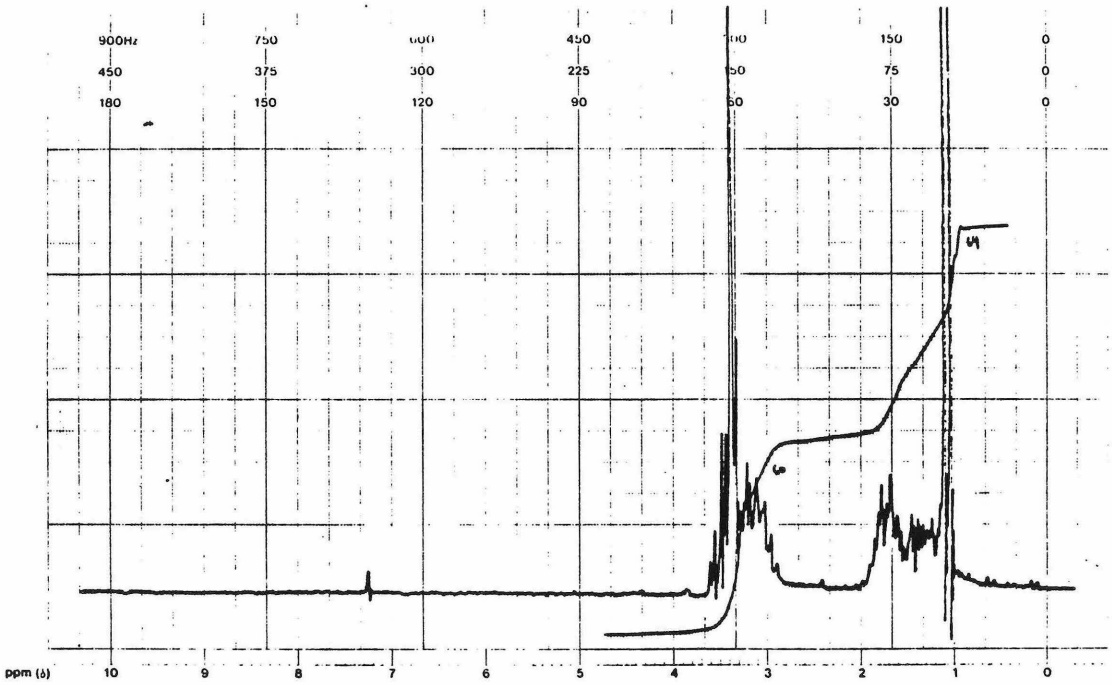


Page 115

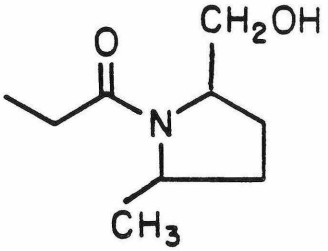


Neat

$CDCl_3$

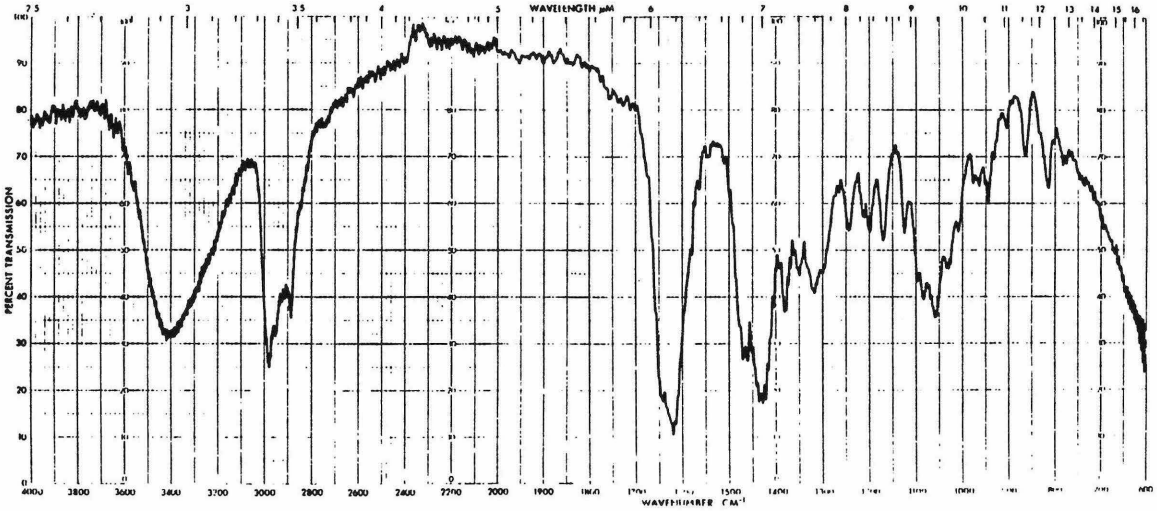


Page 116

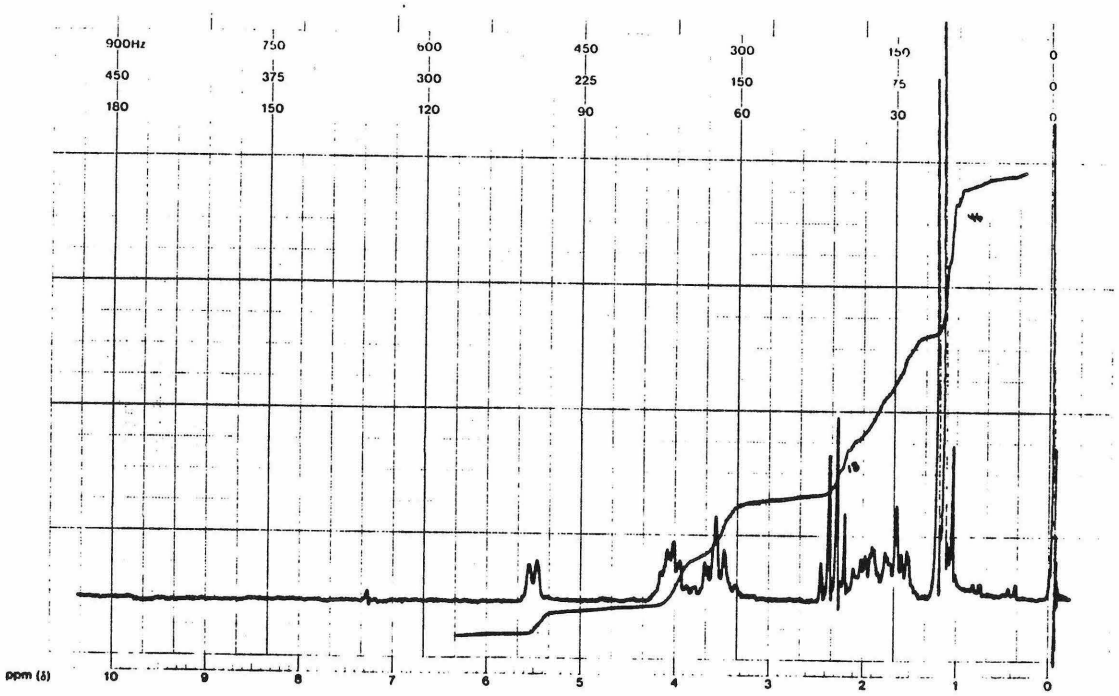


38

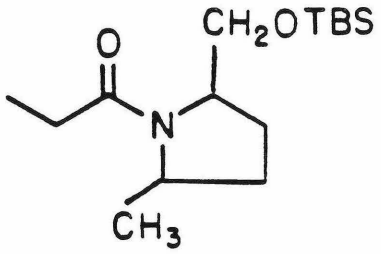
Neat



$CDCl_3$

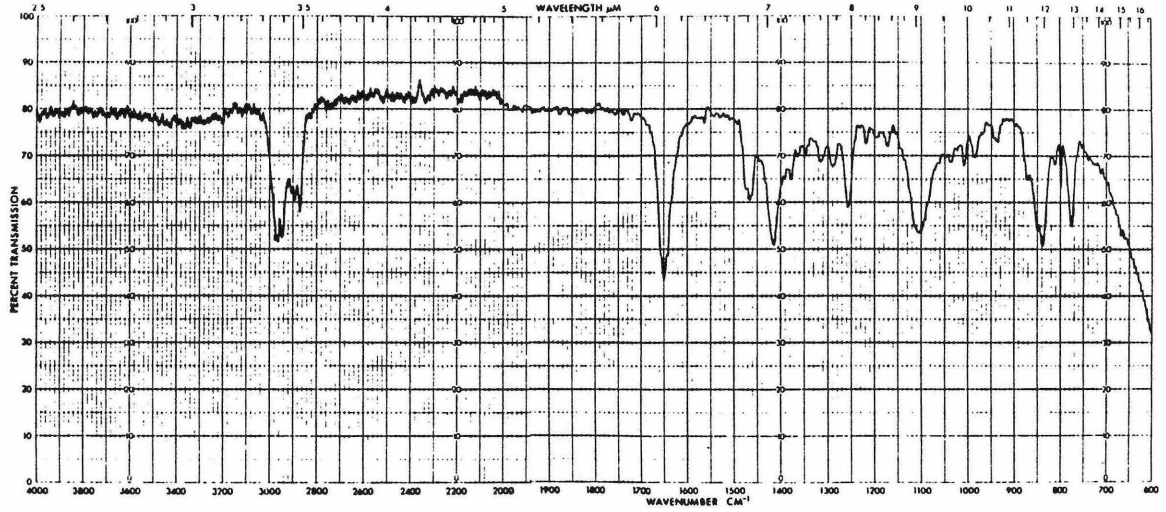


Page 116

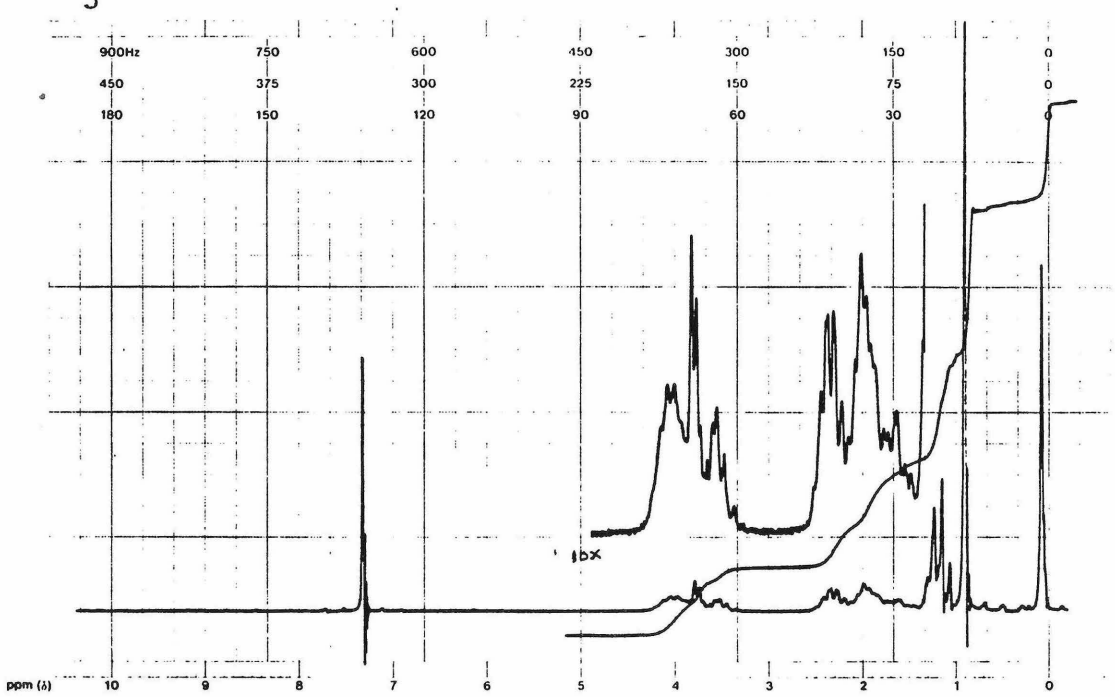


39 41

Neat



$CDCl_3$



VII. PROPOSITIONS

PROPOSITION I.

Approaches to asymmetric synthesis are described, focusing on reactions which,in destroying the symmetry of a molecule containing a symmetry plane,reveal one or more asymmetric centers.

PROPOSITION II.

A new approach to reversing the normally observed regioselectivity of 4+2 cycloadditions through the use of transition metal catalysis is described.

PROPOSITION III.

A convergent approach to the synthesis of the macro-bridged macrocyclic alkaloids ephedradine A,B,C, and aphel-andrine is described. The ephedradines, isolated from the root of a plant used in oriental folk medicine, possess sign-ificant hypotensive activity.

PROPOSITION IV.

Experiments are described to define the factors which control changes in cation binding selectivity as induced by reversible chemical changes in the ligand remote to the ligating centers. The ligands serve as simple models for selective ion transport catalysis. A simple test for eval-

uating chiral ligands with regard to the complex dissociation rate is also described.

PROPOSTION V.

An approach to the syntheisi of asteltoxin, a mycotoxin produced by Aspergillus stelatus, is described. All stereocenters are efficiently controlled relative to the C_3 carbinol.

PROPOSITION I

Approaches to asymmetric synthesis are described, focusing on reactions which in destroying the symmetry of a molecule containing a symmetry plane reveal one or more asymmetric centers.

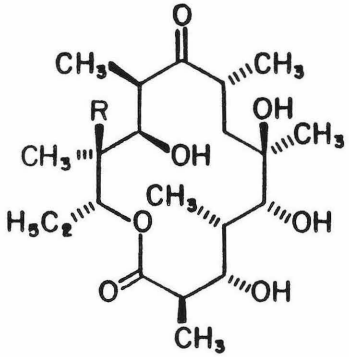
* * * * * * *

A current trend in organic chemistry is toward the synthesis of stereochemically complex natural products. Among the common targets are the highly biologically active ionophore and polyether antibiotics.[1] The synthetic efforts toward these molecules has directed a great deal of attention to the control of acyclic stereochemistry and new methods of asymmetric induction.[2] These methods for asymmetric synthesis focus on three general areas of: 1) the development of methods used in the construction of carbon-hydrogen, carbon-carbon and carbon-heteroatom bonds including efficient control of absolute configuration at the newly formed centers;[3] 2) the efficient utilization of the asymmetric centers of readily available chiral molecules as subunits in the conversion to the desired products;[4] and 3) the efficient mechanical resolution of small precursor molecules.[5]

In examining these classes of antibiotics we were struck by the fact that in spite of the number of asymmetric centers, these structures contain high levels of local symmetry in their backbones. The examples depicted in Scheme I isolate some of the local elements of symmetry which comprise a relatively large portion of the target structure. The symmetry within these fragments is disrupted, and hence the asymmetry is generated, by only differences in oxidation levels of the ends, differences in the terminal substituents or by the pesence of a substituent remote to the backbone. Current approaches to the synthesis of these subunits typically rely on mechanical resolution or a linear synthetic approach using a naturally occurring chiral starting material.

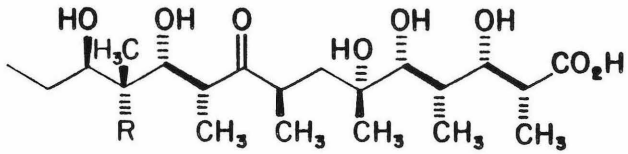
In addressing this problem we have defined a program of asymmetric synthesis focused on reactions with molecules containing a symmetry plane, which in themselves may or may not create a new stereocenter, but which destroy the symmetry of the molecule and reveal one or several new asymmetric centers. The questions we wish to pursue are illustrated phenomenologically by the conversion of either symmetric molecule **1** or **2** to the β-hydroxypropionic acid **3** (Scheme II). Converisons of this type are well known in biosynthesis[6]

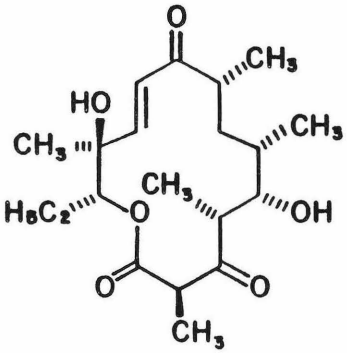
Scheme I



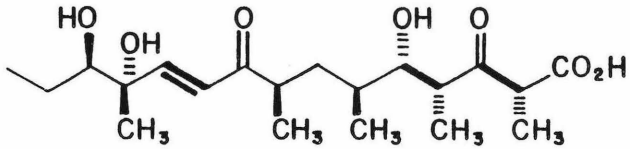
erythronolide

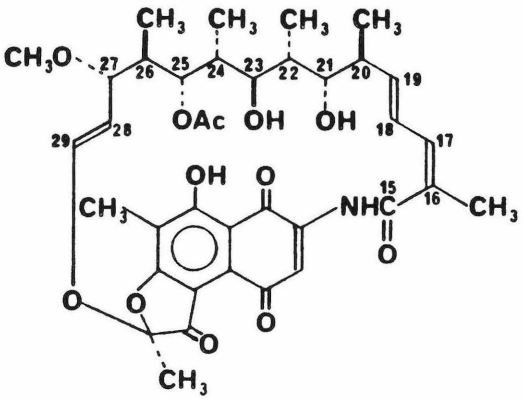
A: R = OH
B: R = H



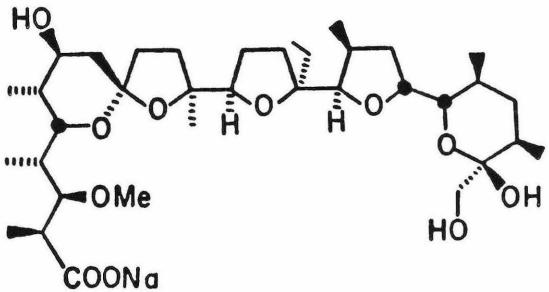


pikromycin



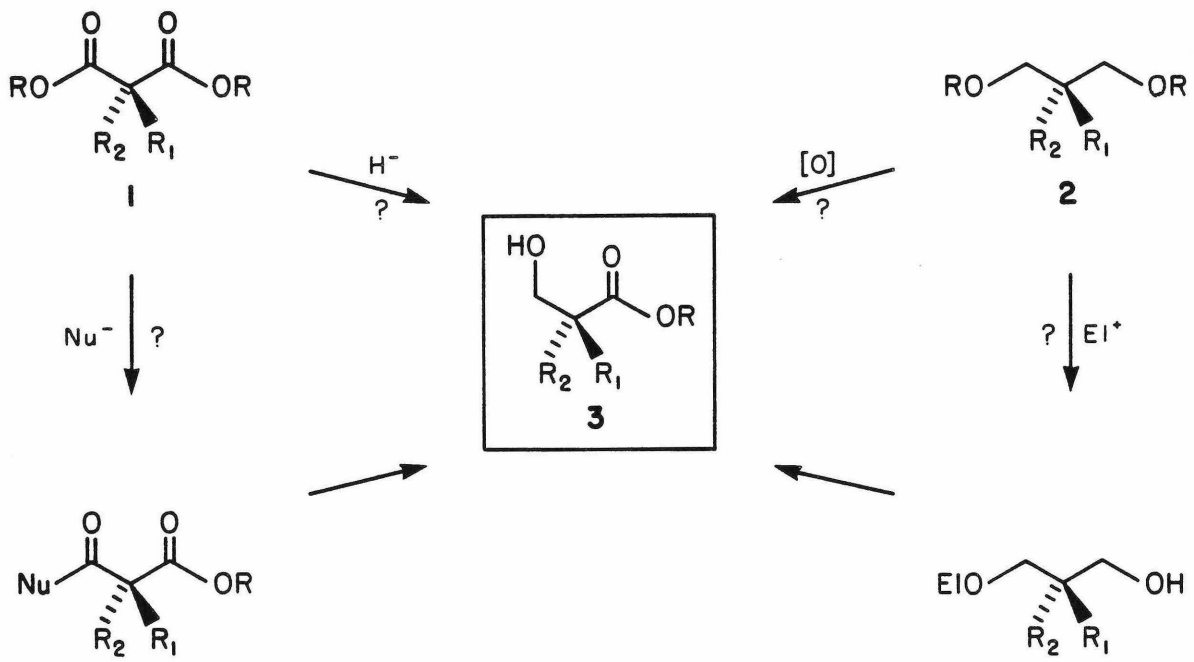


rifamycin.



monensin

Scheme II



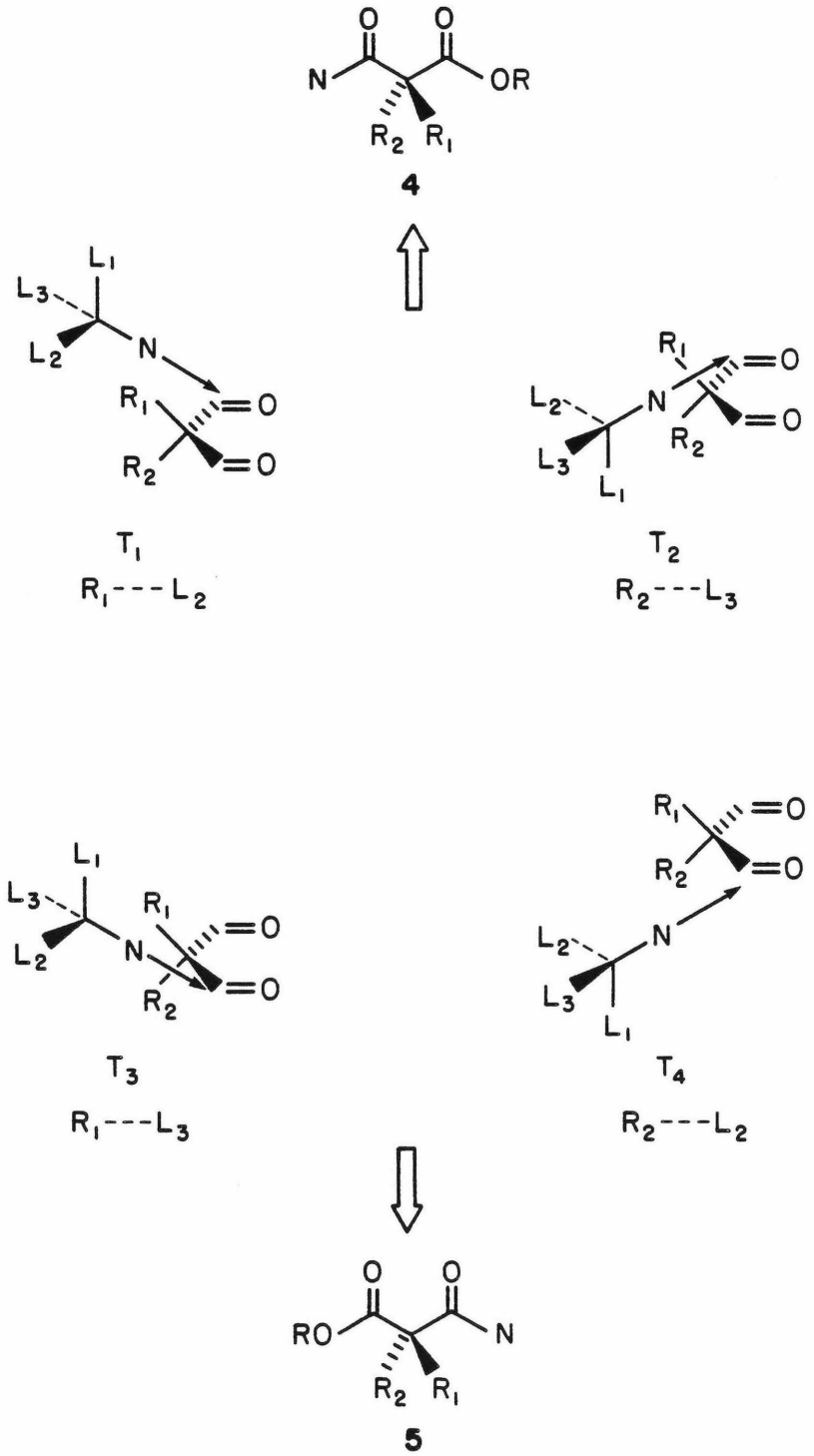
and are being explored with unnatural substrates using enzymatic preparations.[7] Approaches to this in the laboratory have, however, had limited success.[8]

If successful, development of this methodology to induce asymmetry would represent a simple approach to the ionophore antibiotics which both recognizes and utilizes the concept of local symmetry in defining convergent bond disconnections. Typically asymmetric

reactions set the chirality at only one or two centers with each bond construction. Thus, if three independent centers are constructed, each with 90% efficiency, the overall stereochemical yield is 70%. In the present approach asymmetry is revealed at several centers in a single bond construction minimizing the number of asymmetric reactions that need to be performed and offering potential for both high chemical and stereochemical yield. Since the substrate is a symmetric molecule it should be simple to alter the reaction to produce either absolute configuration as needed from the same precursor.

Our approach toward answering the questions posed by Scheme II rely on understanding how to control both ambident reactivity and stereochemistry. It should be possible to develop and apply chiral reagents which discriminate between the subtle differences in diastereotopic transition states to this problem. The four transition states in Scheme III serve to illustrate the control concepts we wish to employ. These four differ with regard to the preferred side of attack [ie., 1,2 diastereoselection, T_1 (T_3) vs T_2 (T_4)] and the nature of the interaction between chiral nucleophile and the resident α-substituent [T_1 (T_2) vs T_3 (T_4), asymmetric carbonyl addition]. Both types of stereoselection have

Scheme III

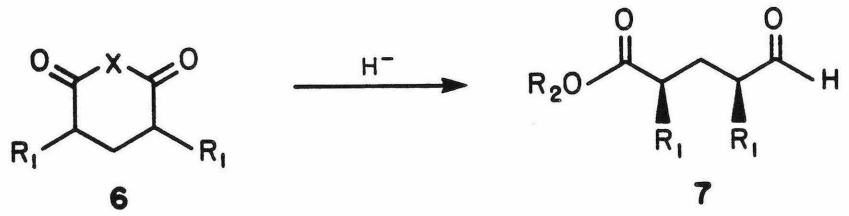


been successfully exploited in synthesis. In the present application, inducing reaction through one of the four possible transition states will insure the regiochemistry of addition and the preferential formation of either 4 or its enantiomer 5. A wide variety of alternative bond construction modes, can be pursued for the realization of this type of enantioselection. For our initial investigation into this area we propose to examine three general types of bond construction.

Reaction of a Chiral Nucleophile With a Symmetric Electrophile. This is the process illustrated in Scheme II. Our initial investigations will focus on the reaction of cyclic anhydrides or the equivalent. Our primary focus will be on those bond constructions with immediate application to the ionophore antibiotic synthesis. The requirements for a successful nucleophile, other than those suggestions in Scheme II, will need to be determined experimentally. In line with this we will examine both the known chiral reagents and from those results, if necessary, design our own.

The acylations of simple chiral alcohols and amines have met with little success ($<$10% ee).[9] Chiral hydride reducing agents have been examined extensively for aldehyde and ketone reductions and in some show high selectivity.[3] One particularly promising reagent for

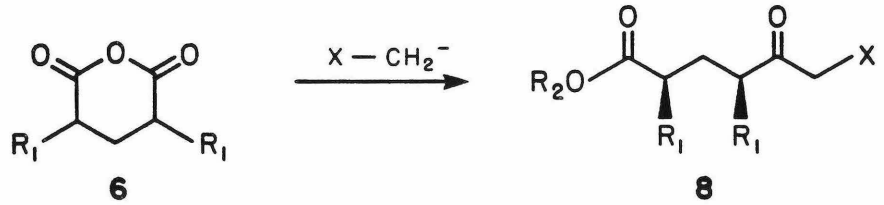
the application in equation 1 is the chiral binapthal complex developed by Noyori. The reduction of 1,4-cyclopent-2-enedione, which embodies many of the same stereochemical problems as the proposed study, proceeds with high efficiency (94-96% ee).[10]



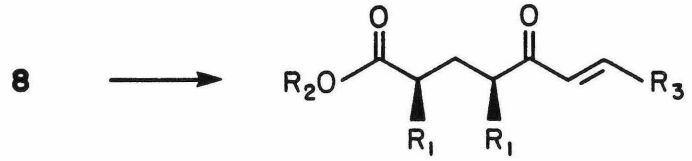
(1)

X = O, S, NR, $C(CH_3)_2$

A second area of focus will concern the addition of stabilized carbanions. Chiral phosphorus[12] and sulfur[13] stabilized carbanions have been explored. Certain of the latter cases show particularly high stereoselection. Wittig substrates in the achiral series often show high regioselectivity in the reaction with ambident electrophiles.[14] These addition products 8 would permit further elaboration as might be required in a Pikromycin or similar synthesis (eq 2, 3).

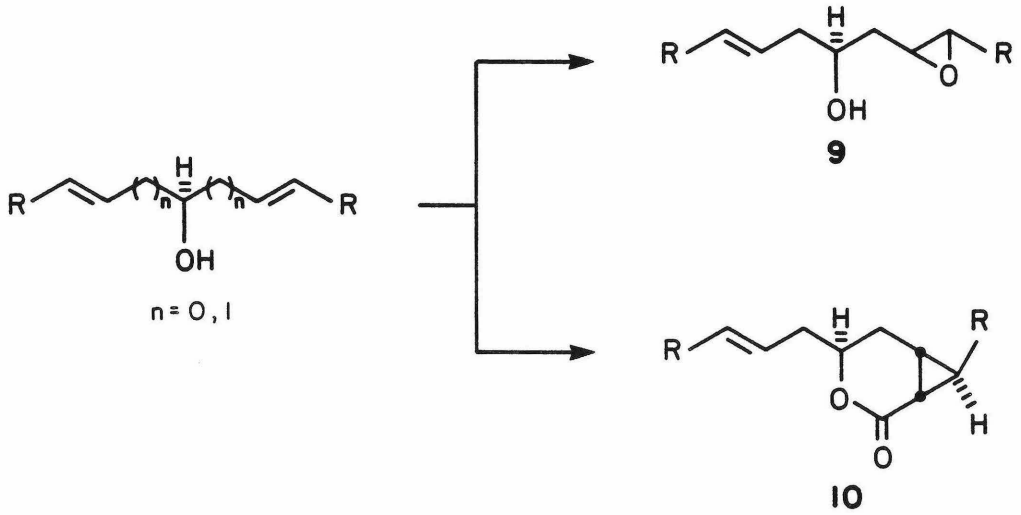


(2)



(3)

Reaction of a Chiral Electrophile Reagent With a Symmetric Nucleophile. Nucleophile Olefins. The recent reports of aysmmetric epoxidations[15] and cyclopropanations[16] should be applicable to symmetric dienes of the type illustrated in equations 4 and 5. One of the cyclopropanation catalysts has been successfully applied to

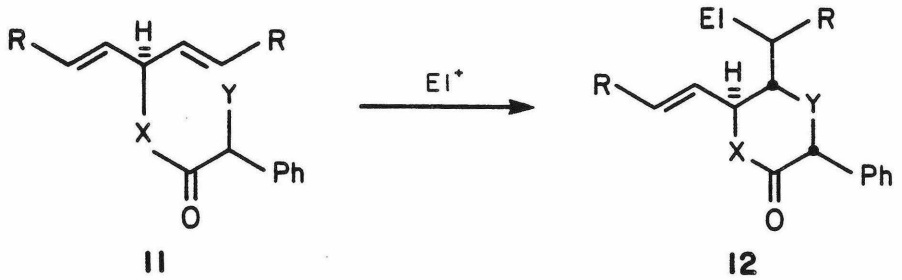


(4)

(5)

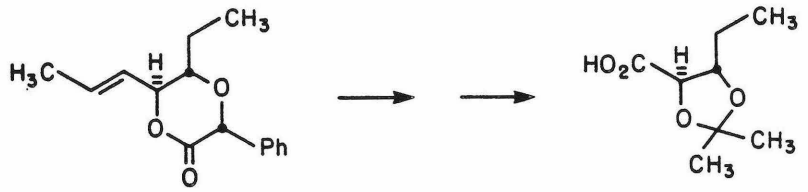
the symmetric conjugated diene, 2,5-dimethyl-2,4-hexadiene (>60% ee). The present applications can be performed in a intramolecular sense and may show even higher selectivity. The Sharpless epoxidation procedure is reported to be applicable to the kinetic resolution of allylic alcohols and hence useful intermediates of tye type 9 and 10 (n_1 = 0, 1) should be readily available.

The substrates illustrated in equation 6 have yet to be tested but may well extend the methods for oxy-metallation and halolactonization to the differentiation of symmetric substrates. This approach if successful could offer a good deal of generality and flexibility



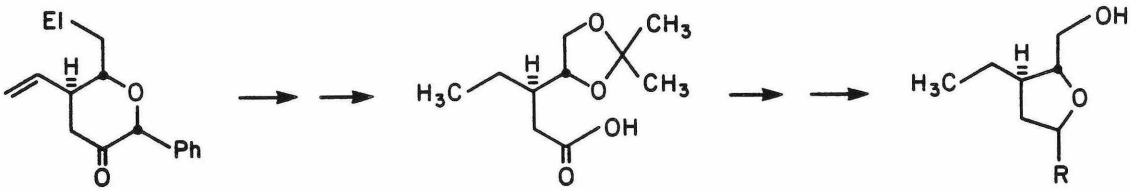
(6)

for the preparation of simple chiral subunits. Potential applications of the mandelic acid derived substrates are suggested in equations 7 and 8. Removal of the chiral auxiliary, protection of the diol and reaction of the



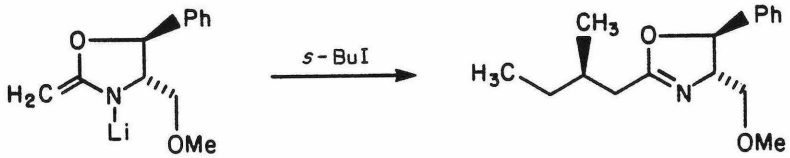
(7)

13



(8)

14

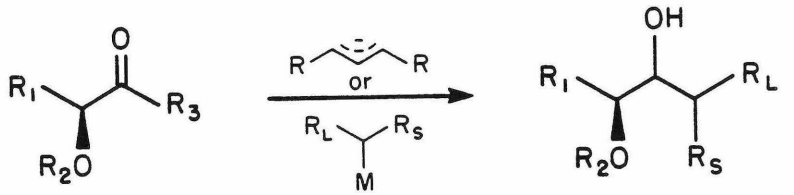


(9)

double bond could ultimately lead to the functionalized diol 13 or furan 14.

Reaction of a Chiral Electrophile With a Symmetric Nucleophile. Electrophilic Olefins and Carbonyls. This area of asymmetric synthesis has been largely unexplored. We will examine the influence of a resident chiral center on the stereochemistry in addition of a secondary or allylic carbanion. Even though secondary carbanions are not planar, the enantiomer forms are readily interconverted through a symmetric intermediate. Conceptually these ideas are similar to the kinetic resolution of a racemic

secondary iodide by alkylation of a chiral nucleophile (eq 9).[7] Here we attempt to kinetically resolve the carbanion.[18] The types of bond construction for initial investigation are summarized in equations 10-12 (X_C = chiral auxiliary). The substrates we will examine have



(10)

(11)

(12)

all been shown useful for other types of asymmetric induction. Successful development of the present proposal should significantly extend their utility. For example, equation 12 suggests a way to induce asymmetry while cleaving a chiral auxiliary. This could be used sequentially after performing equation 11 or another independent bond construction.

Successful development of the simple concepts and chemistry described in the research program above should find significant application in asymmetric synthesis. The approach employs novel uses of asymmetric reactions and will require a thorough study and understanding of the factors which control preferential reaction through one of several diastereotopic transition states. Development of these concepts should open up numerous similar applications.

References and Notes

1. (a) Westley, J.W. Adv. Appl. Microbiol., 1977, 22, 177-223.

(b) McGlocklin, S; Eisenberg, M. Annu. Rev. Bioeng., 1975, 4, 335-366.

2. Bartlett, P.A. Tetrahedron, 1980, 36, 2-72.

3. ApSimon, J.W.; Seguin, R.P. Tetrahedron , 1979, 35, 2797-2842.

4. Hanessian, S. Accts. Chem. Res. , 1979, 12, 159-165.

5. (a) Meyers, A.I.; Slade, J.; Smith, K.; Mihelich, E.D.; Hershenson, F.M.; Liang, C.D. J.Org. Chem., 1979, 44, 2247-2249.

(b) Pirdle, W.H.; House, D.W. Ibid., 1979,44, 1957-1960.

(c) Helmachen, G.; Nill, G. Angew. Chem. Int. Ed. Eng., 1979, 18, 65-66.

(d) Ade, E.;Helmachen, G.; Heiligenmann, G. Tetrahedron Lett., 1980, 21, 1137-1140.

6. (a) Hill, R.K.; Rhee, S.W.; Leete, E.; McGraw, B.A. J. Am. Chem. Soc., 1980, 102, 7344-7348.

(b) Overton, K.H. Chem. Soc. Rev. , 1979, 8, 447.

(c) see also: Ranganathan, D.; Ranganathan, S. "Art in Biosynthesis", Academic Press, New York, 1976.

7. For example see:

(a) Furstoss, R.; Archelas, A.; Waegell, B. Tetrahedron Lett., 1980, 21, 451-454.

(b) May, S.W.; Phillips, R.S. J. Am. Chem. Soc., 1980, 102, 5983-5984.

(c) Jakovac, I.J.; Ng, G.; Lok, K.P.; Jones, J.B J. Chem. Soc., Chem. Commun. , 1980, 515-516.

(d) Davies, J.; Jones, J.B. J. Am. Chem. Soc. , 1979, 101, 5405-5410.

8. (a) Trost, B.M.; Curran D.P. J. Am. Chem.Soc., 1980, 102, 5699-5700.

(b) Whitesell, J.K.; Felman, S.W. J. Org. Chem., 1980, 45,755-756.

(c) Daffe, V.; Fastrez, J. J. Am. Chem. Soc., 1980, 102, 3601-3605.

(d) Shimizu, I.; Naito, Y.; Tsuji, J. Tetrahedron Lett., 1980, 21, 487-490.

(e) Hoffmann, R.W.; Gerlach, R.; Goldmann, S. Chem. Ber., 1980, 113, 856-863.

(f) Terashima, S.; Sato, S.; Koga, K. Tetrahedron Lett., 1980, 21, 3469-3472.

(g) Trost, B.M.; Shuey, C.D.; DiNinno, Jr.,F.; McElvain, S.S. J. Am. Chem. Soc. , 1979, 101, 1284-1285.

9. Morrison, J.D.; Mosher, H.S. "Asymmetric Organic Reactions", American Chemical Society; Washington, D.C.,

1976, 419-424.

10. (a) Nishizawa, M.; Noyori, R. Tetrahedron Lett., 1980, 21, 2821-2824; and references there in.

(b) Noyori, R. First Symposium on Synthetic Organic Chemistry, Kyoto, Japan, September 1980.

11. For example see: Masamune, S.; Ali, S.A.; Snitman, D.L.; Garvey, D.S. Angew. Chem. Int. Ed. Eng., 1980, 19, 557-558.

12. (a) Tomoskozi, I.; Janzso, G. Chem. Ind. (London) , 1962, 2085.

(b) see also reference 8a.

13. (a) Mioskowski, C.; Solladie, G. Tetrahedron, 1980 36, 227-236.

(b) Colombo, J. Chem. Soc., Chem Commun. ,1979, 591.

14. (a) Ingham, C.F.; Massy-Westroff, R.A.; Reynolds, G.D.; Thorpe, W.D. Aust. J. Chem. , 1975, 28, 2499-2510.

(b) Giannella, M.; Gualtieri, F.; Melchiorre, C. J. Org. Chem. , 1974 , 39, 3048-3050.

(c) Gossauer, A.; Hinze, R.P.; Zilch, H. Angew Chem. Int. Ed. Eng., 1977, 16, 418.

(d) Flitsch, W.; Müter, B. Chem. Ber., 1977,104,2852-2855.

15. Katsuki, T.; Sharpless, K.B. J. Am. Chem. Soc., 1980, 102, 5974-5976.

16. (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. Tetrahedron Lett., 1975, 1707-1710.

(b) Nakamura, A.; Konishi, A.; Tsujitani, R.; Kudo, M.; Otsuka, S. J. Am. Chem. Soc. , 1978, 100, 3449 (78).

17. Meyers, A.I.; Kamata, K. J. Am. Chem. Soc., 1976, 98, 2290-2294.

18. (a) Tamao, K.; Hayashi, T.; Matsumoto, H.; Yamamoto, H.; Kumada, M. Tetrahedron Lett. , 1979, 2155-2156.

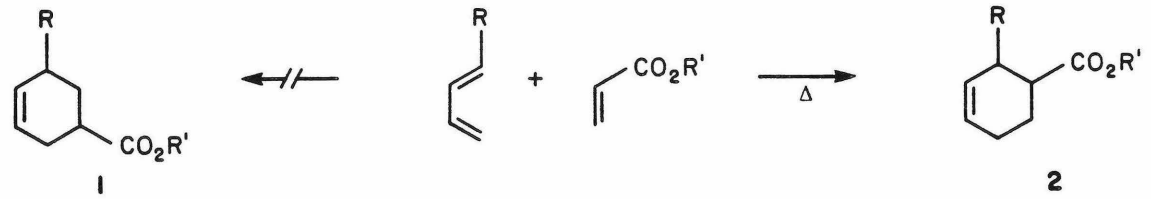
(b) Still, W.C.; Sreekumar, C. J. Am. Chem. Soc. , 1980, 102, 1201-1202.

PROPOSITION II

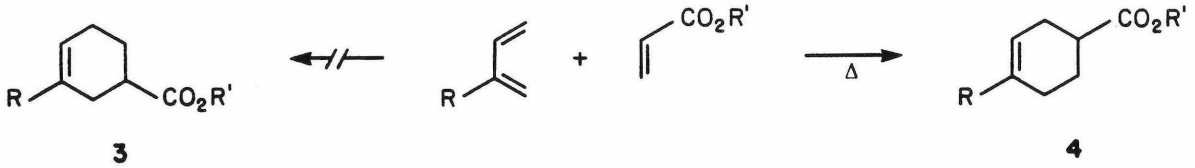
A new approach to reversing the normally observed regioselectivity of 4+2 cycloadditions through the use of transition metal catalysis is described.

* * * * * * *

The Diels-Alder cycloaddition is perhaps the most powerful reaction in the arsenal of the synthetic organic chemist for the control of regio- and stereochemistry. It has been used as the foundation of innumerable total syntheses and as a cornerstone in retro-synthetic analysis and synthesis design.[1] The unique control of regiochemistry, which has been explained on the basis of orbital overlap, yields products resulting from predominantly one of the two possible orientations of diene and dieneophile (eq 1, 2).[1e] This regioselectivity provides perhaps the greatest advantage and yet the greatest limitation of the Diels-Alder reaction. We have for some time been interested in ways to selectively obtain products resulting from the opposite orientation (**1**, **3**), which should significantly expand the synthetic utility of this process.



(1)



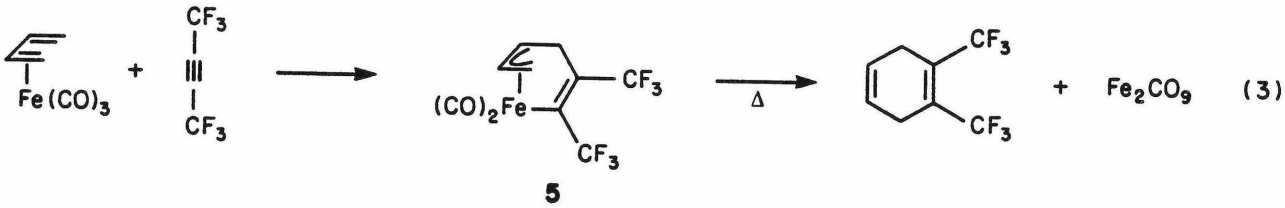
(2)

Aside from certain of the inverse electron-demand reactions, the approaches to the so-called "meta-Diels-Alder" products (1, 3) have centered on strategies which either: 1) convert the normal selectivity pattern obtained into the desired product by a second chemical process involving rearrangements or bond cleavages;[3] or 2) constrain the orientation by connecting the diene to the dieneophile and performing an intramolecular reaction.[1a,b] Although synthetically useful, the approaches fail to address the fundamental regiochemical problem. We reason there is a need to significantly change the nature of the transition state for bond construction in order to alter the normal selectivity. The effect of lewis acid complexation with the dieneophile to both catalyze the cycloaddition and reinforce the

normal regioselectivity pattern is now well documented. The transition metal catalyzed cyclodimerization of certain dienes is also well known.[4] Particularly the dimerization of butadiene to 4-vinylcyclohexene which is the industrial precursor to styrene. However, the application of this latter approach to synthetically desirable dieneophiles is largely unknown. We sought to find a diene-metal complex which might react with synthetically useful substrates subject to a much different steric and electronic bias. With regard to this approach, we propose that, at least formally, the solution to obtaining the meta-orientation has already been reported in one example by some Russian workers in 1972.[5] Their work on the reactions of certain iron-diene complexes has gone largely unnoticed because of what we feel has been the misassignment of the regiochemistry obtained from a catalyzed cycloaddition.

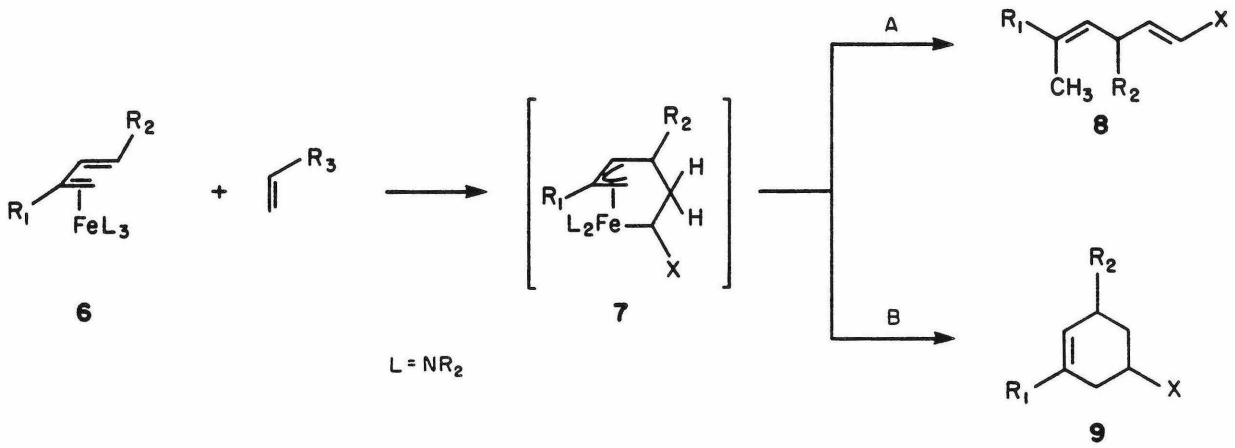
The chemistry of iron-diene complexes has much attention.[6] The work has focused primarily on iron tricarbonyl-diene complexes. Among the wealth of interesting chemistry observed with these substrates are the cycloadditions with acetylenes.[7,8] Crystalline intermediates, 5, derived from oxidative addition and carbon-carbon bond formation have in some cases been examined by X-ray analysis (eq 3).[8] Although similar

intermediates have been observed in the reaction of the iron tricarbonyl derivatives with certain olefins, the reductive elimination does not proceed readily with carbon-carbon bond formation to yield the cycloadduct. The observed reactions depend largely on the nature of the iron catalyst, many of which have not been well characterized.



(3)

In general, reaction of an iron diene complex with an olefin gives a mixture of linear dimers, with the regiochemistry illustrated by 8, resulting from carbon-carbon formation between the 4-position of the diene and 3-position of the dieneophile as in 7. Presumably β-hydride elimination to give a iron hydride which then undergoes reductive elimination to produce 8 (eq 4, Path A).[5,7b,9] The Russian workers[5] observed that in the presence of certain ligands, particularly amines, cycloadducts were obtained in high yield after the reaction had proceeded to relatively low conversion (< 30%). The reaction of isoprene (6, $R_1 = CH_3$, $R_2 = H$) with methyl



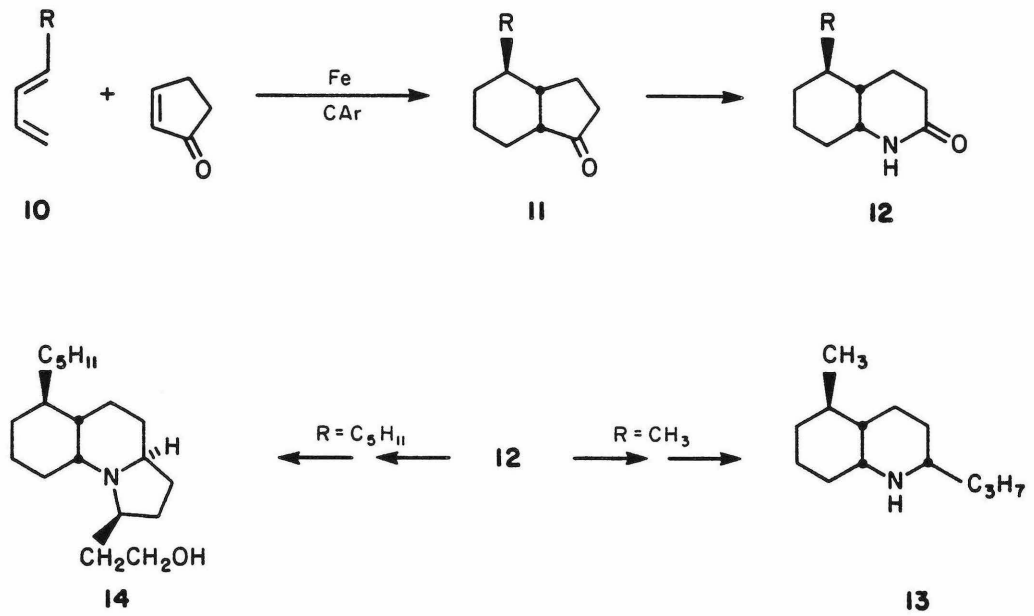
(4)

acrylate (R_3 = CO_2CH_3) was reported to give the product resulting from normal <u>para</u>-orientation, methyl 4-methyl-cyclohex-3-ene-carboxylate, based only on boiling point and refractive index.[10] Based on the evidence which supports 7 as an intermediate in the reaction, we propose the observed product was of the <u>meta</u>-orientation (9, R_1 = H, R_2 = CH_3, R_3 = CO_2CH_3). Corroborating evidence has recently been reported by French workers reinvestigating a nitrogen ligated iron catalyst for butadiene cyclo-dimerization. Dimerization of piperylene (6, R_1 = H, R_2 = CH_3) gave the cycloadduct 9 (R_1 = H, R_2 = CH_3, X = $CH{=}CHCH_3$).

We propose to reinvestigate the original Russian report as well as other iron catalyst systems to determine the correct regio- and stereochemistry from the cycloadditions of synthetically useful substrates. Regardless of the regiochemistry, the correct assignment is mechanistically important because of the economic significance of metal catalyzed diene cyclodimerization.[4] The catalyzed cycloadditions will be optimized in terms of yield and generality to render these reactions synthetically useful. Also, irrespective of the observed regiochemistry, these metal catalyzed cycloadditions offer through the utilization of metal centered steric effects for inducing asymmetry catalyzed asymmetric carbon-carbon bond formation is perhaps the most efficient and highly sought after form of asymmetric synthesis. The incorporation of chiral ligands at the reactive metal center of what would seem to be relatively well ordered intermediate 7 (L = chiral ligand) offers an interesting new approach to asymmetric Diels-Alder cycloadditions.[13] Note that the 2,3'-bipyridyl ligand was the most effective studied by the Russian workers for promoting the cycloaddition relative to linear dimerization.[5] Chiral bidentate phosphorus and nitrogen ligands are readily available.[14]

Successful development of this methodology should find widespread application in organic chemistry for the

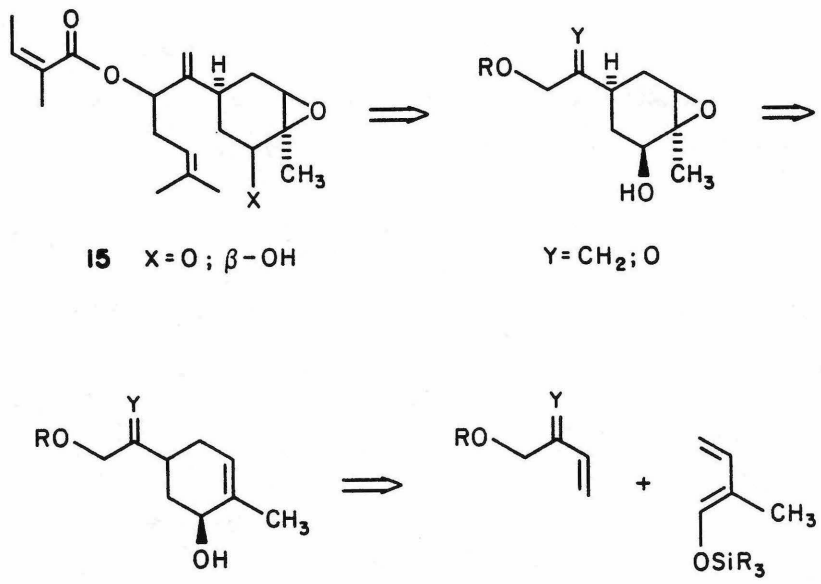
Scheme I



synthesis of stereochemically complex natural products. Some potential applications, based totally on speculated regio- and stereochemistry, are illustrated in Schemes I and II. Addition of piperylene (10, R = CH_3) to cyclopentenone to give 11 which has been carried on to Pumiliotoxin C 13. The original synthesis of 11 was carried out in six steps using an intramolecular 4+2 cycloaddition.[15] Similarly, reaction of 10 (R = C_5H_{11}) might provide, after Beckmann rearrangement, an efficient route to lactam 12 (R = C_5H_{11}) which would tie into and significantly shorten a recently reported synthesis of perhydrogephrotoxin 14.[16] A simple approach to the ring system of some bisabolen sesqueterpene derivatives 15

projected from the above mentioned methodology is outlined in Scheme II.[17]

Scheme II



References and Notes

(1) (a) Oppolzer, W. Angew. Chem. Int. Ed. Engl. 1977, 16, 10-23. (b) Carlson, R. G. Ann. Rep. Med. Chem. 1974, 9, 270-279. (c) Sauer, J. Angew. Chem. Int. Ed. Engl. 1966, 5, 211-229. (d) Titon, Y. A. Russ. Chem. Rev. 1962, 31, 267-283. (e) Hosomi, A.; Saito, M.; Sakurai, H. Tetrahedron Lett. 1980, 21, 355-358.

(2) In part this proposal was originally included as partial fulfillment of the requirements for the Candidacy Exam. Caltech, March, 1978.

(3) Trost, B. M., Ippen, J.; Vladuchick, W. C. J. Am. Chem. Soc. 1977, 99, 8116-8117, and references therein.

(4) Heck, R. F. "Organotransition Metal Chemistry"; Academic Press: New York, 1974; Chapter 6.

(5) Akhmedon, V. M.; Mardanov, M. A.; Zakharkin, L. I. J. Org. Chem. USSR 1972, 8-, 1825-1829.

(6) (a) Birch, A. J.; Raverty, W. D.; Stephenson, G. R. Tetrahedron Lett. 1980, 21, 197-200. (b) Yunker, M. B.; Fraser-Reid, B. J. Org. Chem. 1979, 44, 2742-2745. (c) Noyori, R.; Nishizawa, M.; Shimizu, F.; Hayakawa, Y.; Maruoka, K.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. J. Am. Chem. Soc.

1979, 220-222.

(7) (a) Genet, J. P.; Ficini, J. Tetrahedron Lett. 1979, 1499-1502. (b) Carbonarco, A.; Greco, A.; Dall'asta, G. J. Organomet Chem. 1969, 20, 177-186.

(8) (a) Bond, A.; Lewis, B.; Green, M. J. Chem. Soc., Dalton Trans. 1975, 1109-1118. (b) Green, M.; Lewis, B.; Daly, J. J.; Sanz, F. Ibid 1975, 1118-1127. (c) Bottrill, M.; Goddard, R.; Green, M.; Hughes, R. P.; Lloyd, M. K.; Lewis, B.; Woodward, P. J. Chem. Soc., Chem. Commun. 1975, 253-255. (d) Davis, R.; Green, M.; Hughes, R. P. Ibid 1975, 405-406.

(9) Tolstikov, G. A.; Dzhemilev, U. M.; Khusnutdinov, R. I.; Zelenova, L. M. J. Org. Chem., USSR 1976, 12, 307-310.

(10) (a) As evidenced from the data below, the index of refraction cannot be used as structure proof.

(b)

Ref.	Para:Meta	bp(mm)	n_D^{20}
5	100:	80-81(70)	1.4640
10c	100:	91-92(20)	1.4621
10d	5.4:1	85-88(14)	1.4540
10d	3.8:1	91-92(20)	1.4660
10d	2:1	88-90(16)	1.4655
10d	1.4:1	90-93(20)	1.4642

(c) Inukai, T.; Kasai, M. J. Org. Chem. 1965, 30, 3567. (d) Nazarov, I. N.; Titov, Y. A.; Kuznetsova, A. I. Bull. Acad. Sci., USSR, Div. Chem. Sci. 1959, 1362.

(11) Leroy, E.; Huchette, D.; Mortreux, A.; Petit, F. Nouv, J. Chim. 1980, 4, 173-178.

(12) Candlin, J. P.; Janes, W. H. J. Chem. Soc. (C) 1968, 1856-1860.

(13) (a) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; American Chemical Society: Washington, D. C., 1976, p. 252-258. (b) Boeckman, Jr., R. K.; Naegely, P. C.; Arthur, S. D. J. Org. Chem. 1980, 45, 753-754. (c) Vedejs, E.; Gadwood, R. C. Ibid 1977, 43, 376-378.

(14) ApSimon, J. W.; Seguin, R. P. Tetrahedron 1979, 35, 2797-2842.

(15) Oppolzer, W.; Fehr, C.; Warneke, J. Helv. Chim. Acta 1977, 60, 48-58.

(16) Overman, L. E.; Fukaya, C. J. Am. Chem. Soc. 1980, 102, 1454-1456.

(17) (a) Bohlmann, F.; Suwita, A. Chem. Ber. 1976, 109, 2014-2020. (b) Bohlmann, F.; Zdlero, C. Phytochem. 1978, 17, 1591-1593.

PROPOSITION III

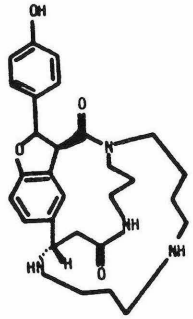
A convergent approach to the synthesis of the macro-bridged macrocyclic alkaloids ephedradine A, B, C and aphelandrine is described. The ephedradines, isolated from the root of a plant used in oriental folk medicine, possess significant hypotensive activity.

* * * * * * *

Alkaloids have long been a focal point for organic chemists. The intense biological activity and diverse structural elements have issued a continual challenge to synthetic endeavors and have been inevitably met with a wealth of interesting, although not necessarily anticipated, chemistry. In light of the interest in the macrolide antibiotics[1] and the physiological importance of the polyamines[2], it is surprising that the macrocyclic alkaloids[3] (Figure I) have only recently begun to receive some attention.[4-6] Of particular interest are the bridged bicyclic alkaloids 7-13 of which the recently isolated ephedradines[7-9] have been shown to possess significant hypotensive activity.

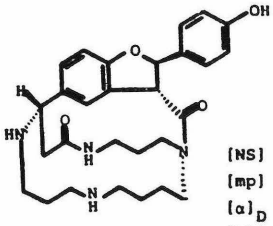
The ephedradines, isolated from the root of a plant used in oriental folk medicine have, as is true with all the macro-bridged bicyclic natural product, yet to be addressed synthetically. In response to the difficulty of isolation,

Aphelandrine $C_{28}H_{36}N_4O_4 \equiv 492$



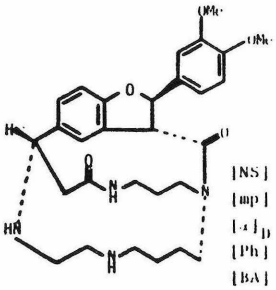
[NS] Chaenorhinum minus
C. villosum
[Ph] IR, NMR, ^{13}C-NMR

Ephedradine B $C_{29}H_{38}N_4O_5 \equiv 522$



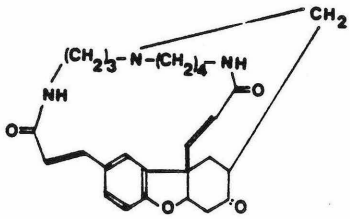
[NS] Ephedra species
[mp] 219 - 221° (hydrobromide)
$[\alpha]_D$ - 101.5° (H_2O)
[Ph] IR, NMR, ^{13}C-NMR, MS, CD

Ephedradine [illegible]

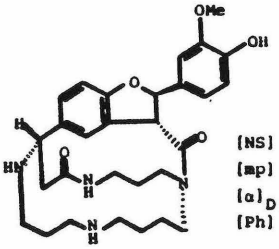


[NS] Ephedra species
[mp] 224 - 225° (dihydrobromide)
$[\alpha]_D$ - 100.7° (H_2O) (dihydrobromide)
[Ph] NMR, ^{13}C-NMR, MS, CD
[BA] Hypotensive activity

ALKALOID LBX
$C_{26}H_{31}O_4N_3$
M.p. 250°C (*dec.*).



Ephedradine B $C_{29}H_{38}N_4O_5 \equiv 522$



[NS] Ephedra species
[mp] 219 - 221° (hydrobromide)
$[\alpha]_D$ - 101.5° (H_2O)
[Ph] IR, NMR, ^{13}C-NMR, MS, CD

CHAENORHINE
$C_{31}H_{40}O_5N_4$
M.p. 263–8°C (*dec.*).

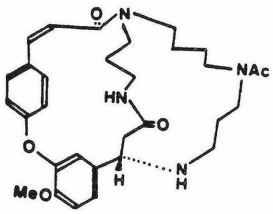


Figure I

the promise of biological activity and the interesting new ring system, we propose the convergent syntheses of ephedradine A and aphelandrine.

Examination of ephedradine A, 7, suggests three subunits, I-III (Figure II), which if handled in a convergent sense would provide maximum flexibility in the synthesis of both naturally occurring compounds and analogs. These subunits define the bond disconnections in a retrosynthetic sense and pose three problems which must be addressed in the total synthesis : 1) construction of the bridge by a macrocyclization process;

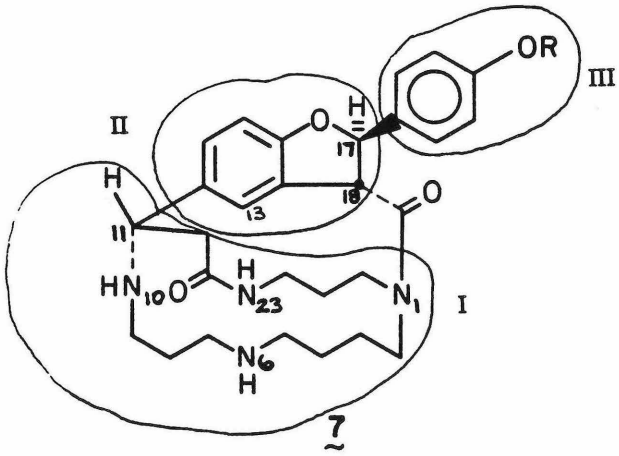
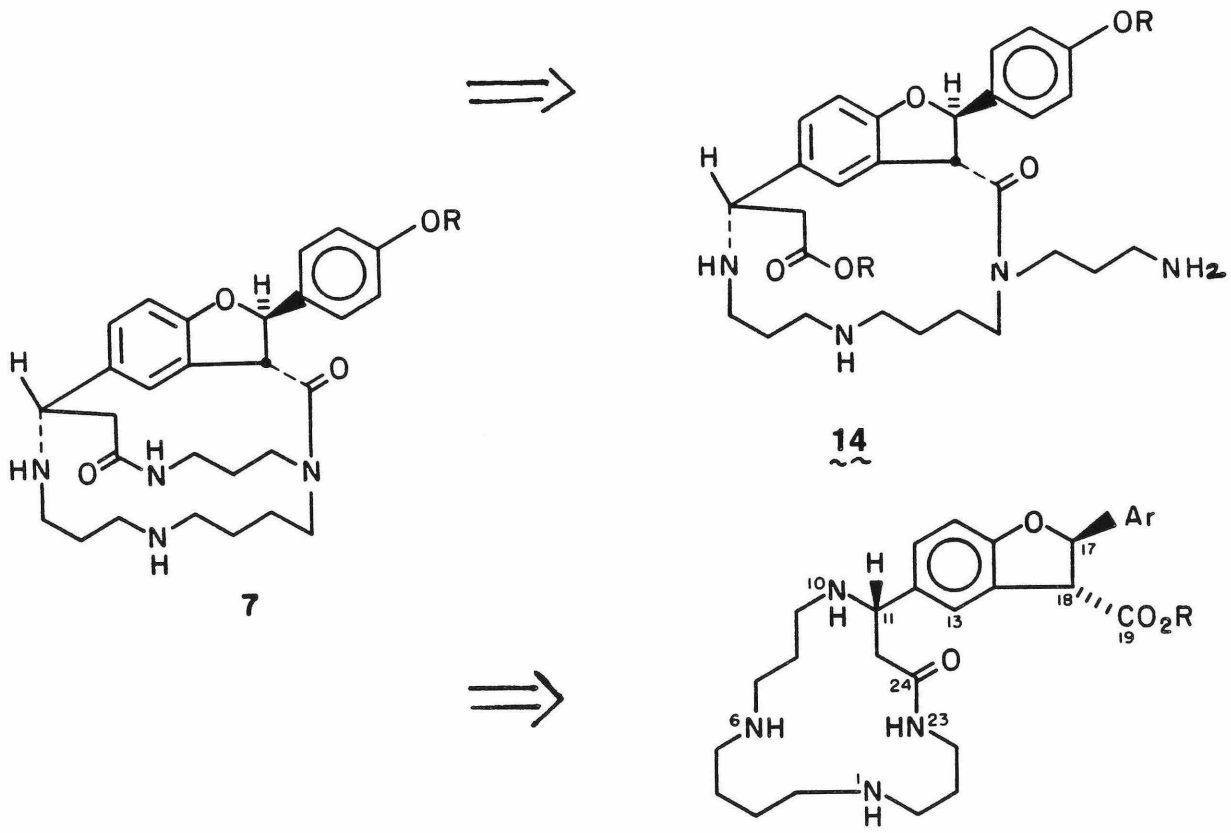


Figure II

2) construction of the macrocyclic lactam ring; and 3) control of stereochemistry between C_{17}, C_{18}, and the remote

stereocenter C_{11}.

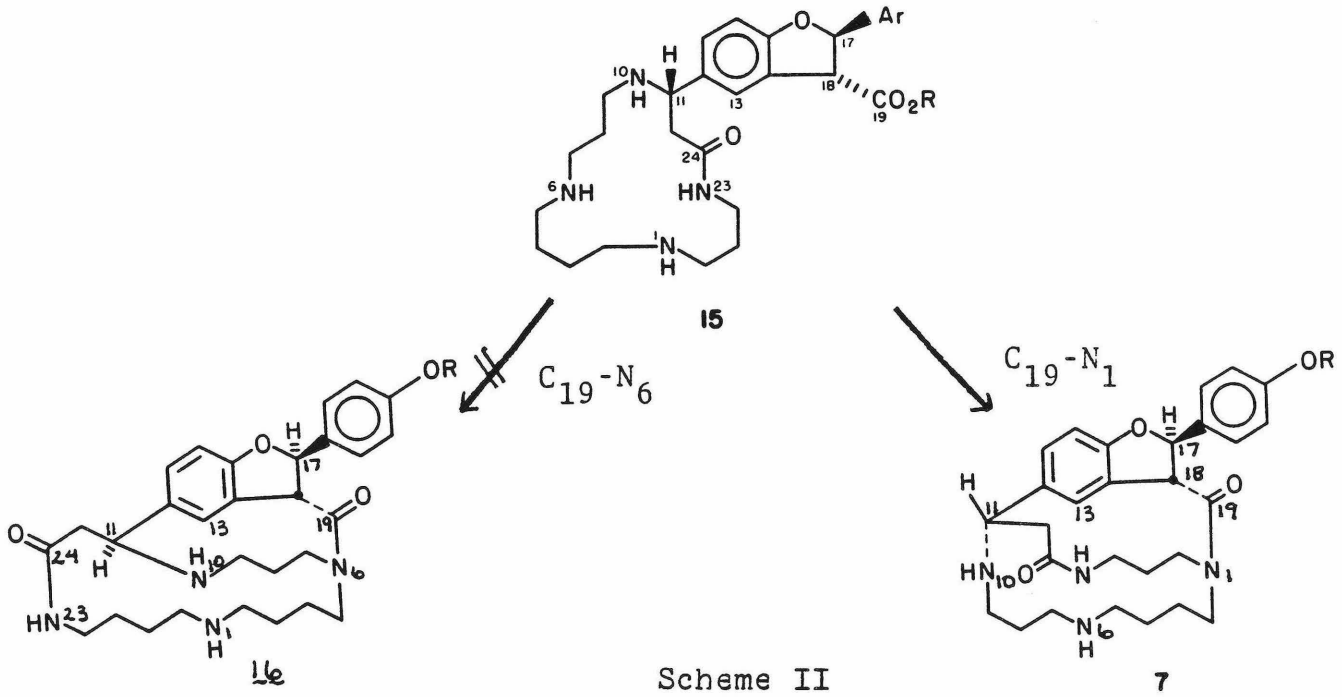
Focusing on the carbon-heteroatom bonds, several alternative disconnections are available for formation of the macrocyclic bridge (7, Scheme I). One can envision using either conjugate addition, N-alkylation or N-acylation to form the bridge. Although all of these reactions have been used extensively in bimolecular or in five and six-membered ring forming reactions applied to alkaloid synthesis, only the lactam formation has been successfully applied to macrocyclization. The two alternative bond disconnections are



Scheme I

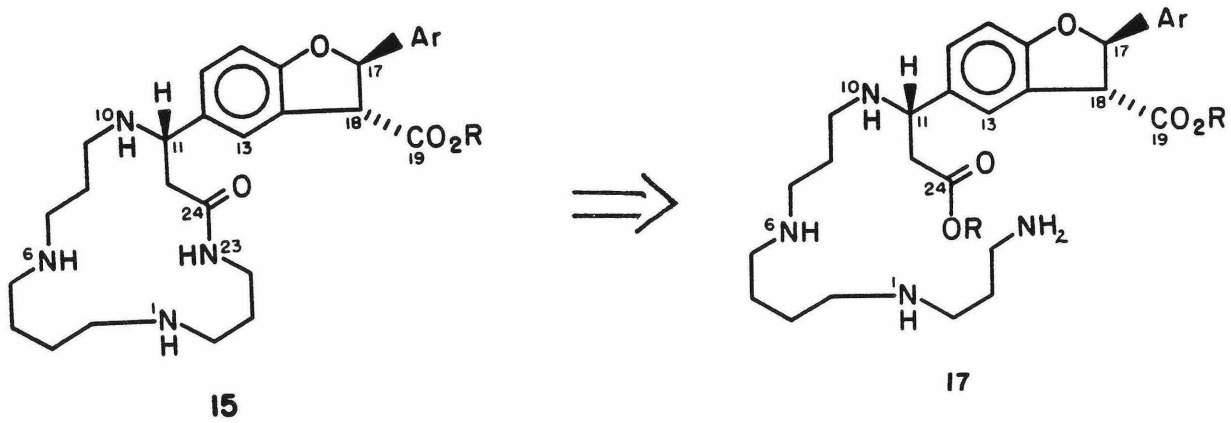
15

outlined in Scheme I. Due to the rather unpredictable conformational effects in large rings it is not possible to predict with any degree of certainty whether closure from the 16-membered ring lactam 14 or from the 17-membered macrocycle 15 would proceed with greater facility. We prefer disconnection D from several lines of reasoning. Proposed intermediate 14 positions the reacting centers C_{24} and N_{23} at the termini of conformationally unconstrained sidechains in contrast to 15 where rotational freedom is restricted. The natural product 7 is known from NMR temperature studies to exist in several relatively discrete conformations which only slowly interconvert at 25°C.[8] Path B attempts closure on to a primary as opposed to the more basic secondary amine.



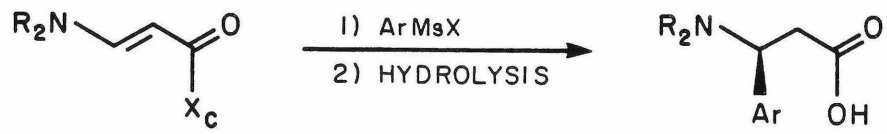
Scheme II

Effecting path B in the synthetic sense would probably require blocking both N_6 and N_{10}, based on limited precedent showing roughly equal facility for 8- and 16-membered ring formation.[10] Consider the two plausible intramolecular closures illustrated in Scheme II. Examination of molecular models reveals that in structure 16 derived from C_{19}-N_6 closure, the hydrogen attached to the C_{13} interacts strongly with the methylene bridge. Thus we propose the cyclization of 15 should lead directly to 7. Compound 15 should itself be available by lactam formation from 17, as summarized in Scheme III. These macrocyclizations can proceed quite well even with relatively simple reagents.[4,5]



Scheme III

The synthesis of 17 embodies the three stereocenters. Control of C_{17} relative to C_{18} under thermodynamic conditions should not be difficult in analogy to work by Jacobson in the synthesis of a similar benzodihydrofuran.[11] Stereochemistry at C_{11} is however, remote and offers no obvious alternative for its control in a relative sense. Typically, one must either accept the mixture resulting from stereorandom synthesis or deal with the construction of each stereocenter independently and with the proper absolute configuration. Although in the present case, asymmetric synthesis may not be warranted from the practical standpoint until more information is available on the biological activity of these molecules, the broader questions are raised on the synthesis of β-amino acids and β-alkoxy acids which are not conveniently prepared by an aldol route. Routes to chiral β-amino acids focusing on 1,4 addition of a nitrogen nucleophile[12] or hydrogenation of N-acyl eneamines have been met with moderate success (-60%ee).[13] A different approach would apply the highly successful work on 1,4 additions of carbon nucleophiles to alkyl substituted α,β unsaturated acid derivatives.[14] Addition to β-amino substituted derivatives should proceed with equal facility (eq. 1). Hootelle has recently reported an example of diastereoselective addition to a β-amino ketone (eq. 2).[15] Successful developement of



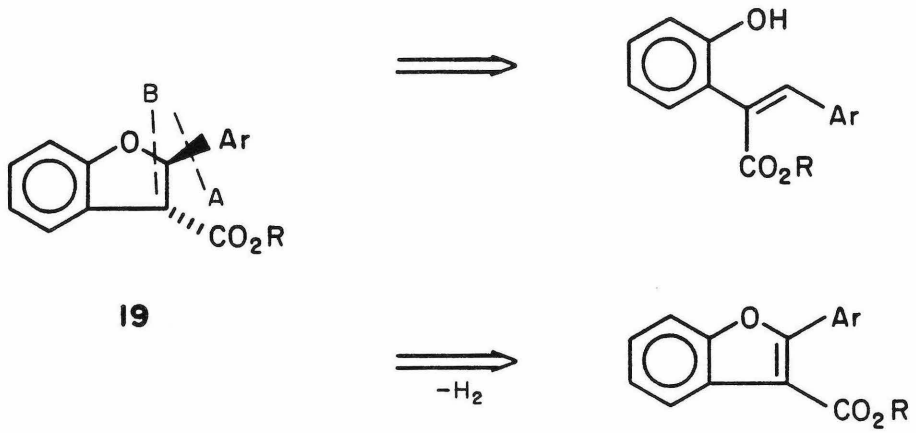
(1)

18

X_c = CHIRAL AUXILLIARY

this methodology would find extensive application in β-lactam, cyclopeptide and alkaloid synthesis.

The β-alkoxy acids, illustrated by the benzofuran derivative 19, present different problems (Scheme IV). The lability toward β-elimination makes an asymmetric 1,4 addition of a carbanion quite speculative. Chiral catalysis of heteroatom 1,4 addition is in some cases quite successful.[16] These reactions are mechanistically complex and the predictive capabilities are as yet quite low. The intramolecular addition proposed in Scheme IV may provide a good system for study of this approach. Studies on natural product 7 reveal that base catalyzed epimerization apparently does not destroy the stereochemistry at the β-carbon.[8] Thus, the cis-furan is also a viable synthon for 19. In that regard, the asymmetric hydrogenation has not been examined.



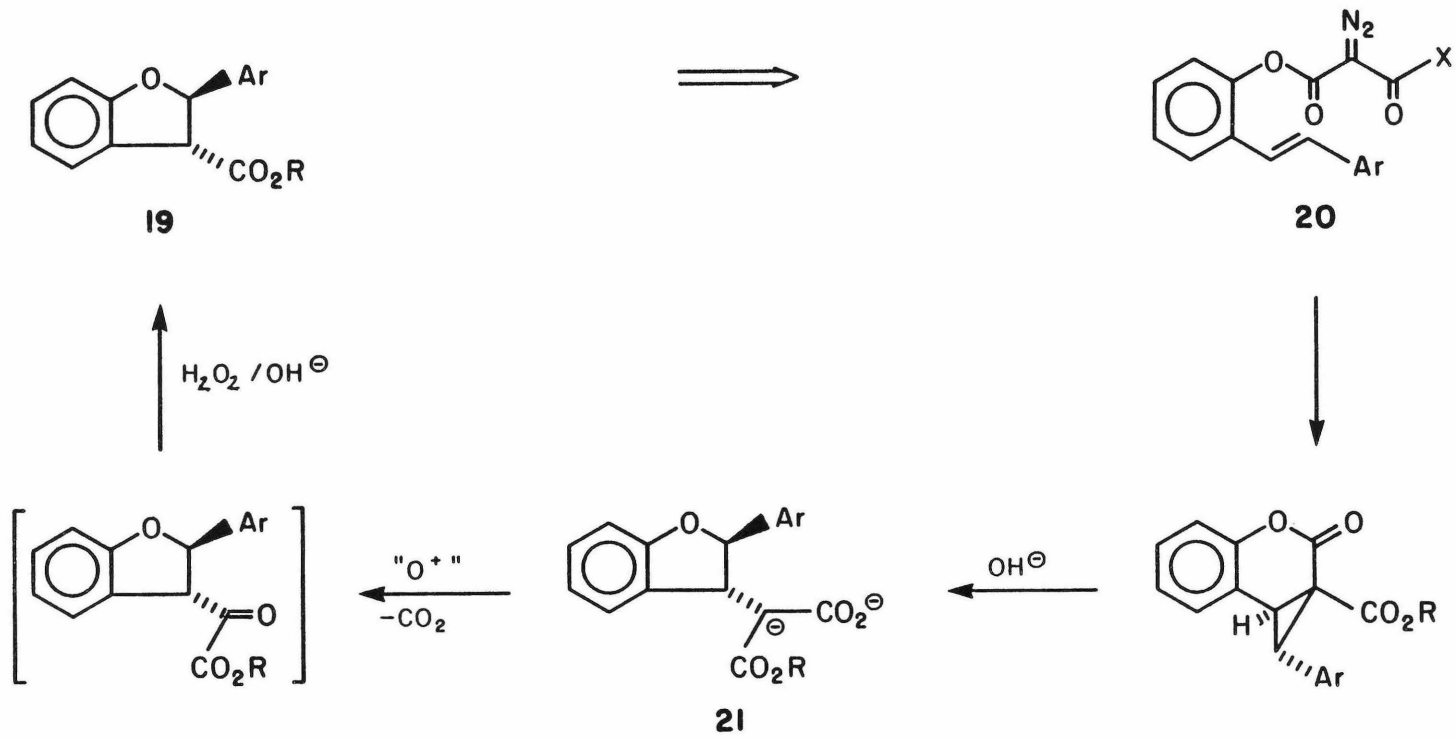
Scheme IV

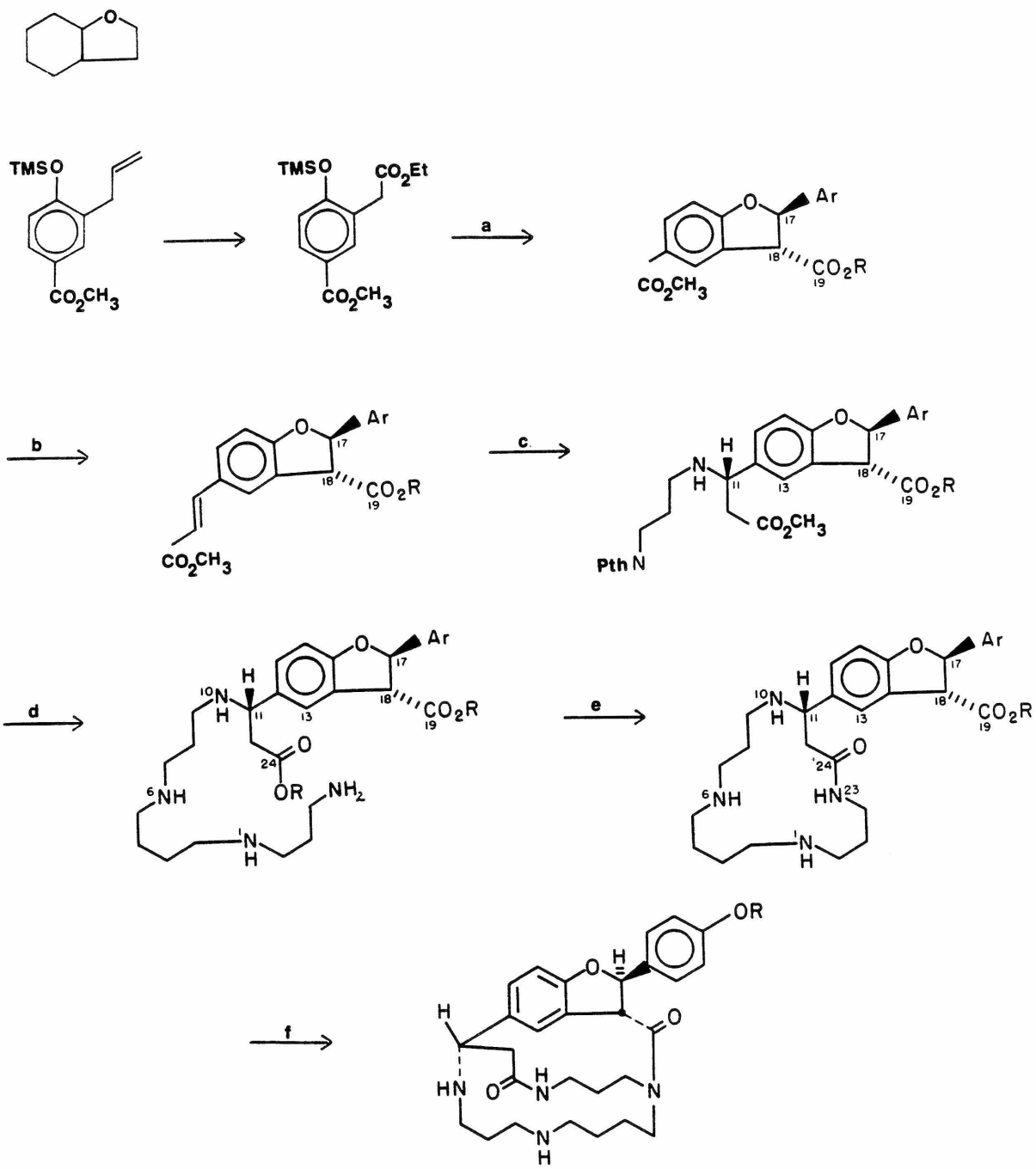
A somewhat different approach is outlined in Scheme V. Asymmetric cyclopropanations using a chiral cobalt catalyst has been performed on a limited range of substrates with high enantioselection (-88% ee)[17]. The reaction which shows a first order dependence on olefin concentration is unsuccessful with trans-disubstituted olefins. Application of this catalytic system in an intramolecular reaction as proposed here has yet to be attempted. This potentially could, through more favorable kinetics, substantially expand the

the scope of substrates for this and related enantioselective cyclopropanations. An alternative approach would study the effectiveness of chiral mixed malonate 20 (X=chiral ester amide) derivatives in the intramolecular cyclopropanation.[18] Hydrolysis of the lactone, intramolecular openning of the activated cyclopropane[19], followed by oxygenation and decarboxylation,[20] should complete a versatile enantioselective route to the benzofuran derivatives. Developement of these methods should provide ready access to a variety of benzofurans, such as the recently synthesized heptamethyl lithiospermate[11], as well as to other furans and pyrans which are important subunits in the polyetherantibiotics.[1]

A synthesis of racemic ephedradine 7 (Scheme VI), which tests the notations discussed in the retrosynthetic analysis, can be pursued concurrent with the proposals for asymmetric synthesis discussed above. The synthesis of methylorantine and ephedradines B and C should follow analogously. Aphelandrine has been obtained by epimerization of ephedradine A.[8]

Scheme V.





Scheme VI.

a) 1. LDA 2. ArCHO 3. Acid cat. 4. H_2 5. Acid cat.
b) 1. PrSLi 2. BH_3 3. CrO_3 4. Wittig c) RNH_2
d) 1. N_2H_4 2. RI 3. N_2H_4 e) 1. PrSLi 2. $(COCl)_2$
f) 1. NaOH 2. $(COCl)_2$

References and Notes

1. (a) Westley,J.W. Adv. Appl. Microbiol. 1977, 22, 177-223.

   (b) McGlocklin,S.;Eisenberg,M. Annu. Rev. Bioeng.,1975, 4, 335-336.

2. (a) Cohen,S.S. "Introduction to Polyamines", Prentice-Hall: Englewood Cliffs, NJ, 1971.

   (b) Anderson,J.N.; Martin, R.O. Phytochemistry, 1973, 12, 443.

   (c) Tabor,H.; Tabor,C.W.; Rosenthal,S.M. Annu. Rev. Biochem., 1961, 30, 579.

   (d) Smith, T.A, Endeavour, 1972, 31, 22.

3. (a) Hesse, M.;Schmid,H. Int. Rev. Sci.,2 , 1976, 9, 265-307.

   (b) Badawi, M.M.; Bernauer,K.; Van Den Broek,P.; Groger, D.; Guggisberg, A.;Johne,S.; Kompis,I.; Schneider,F.; Veith,H.J.; Hesse,M.; Schmid,H. Pure Appl. Chem., 1973, 33,81.

4. McManis,J.S.; Ganem,B. J. Org. Chem., 1980, 45, 2041-2042.

5. Bernhard,H.O.;Kompis,I.; Johne,S.; Gröger,D.; Hesse,M.; Schmid,H. Helv. Chim. Acta, 1973, 56, 1266-1303.

6. (a) Schneider,F.; Bernauer,K.; Guggisberg,A.; Van Den

Broek.P.; Hesse,M.; Schmid,H. Helv. Chim. Acta, 1974, 57, 434.

(b) Guggisberg, A.; Van Den Broek, P.; Hesse, M.; Schmid, H.; Schneider,F.; Bernauer, K. Ibid, 1976, 59, 3013-3025.

7. (a) Konno, C.; Tamada, M.; Endo, K.; Hikino, H. Heterocycles, 1980, 14, 295.

(b) Tamada,M.; Endo, K.; Hikino, H. Ibid. , 1979, 12, 783.

(c) Tamada, M.; Endo, K.; Hikino, H.; Kabuto, C. Tetrahedron Lett. , 1979, 873-876.

8. (a) Dätwyler, P.; Bosshardt, H.; Johne, S.; Hesse, M. Helv. Chim. Acta 1979, 62, 2712.

(b) Dätwyler, P.; Bosshardt, H.; Bernhard, H.O.; Hesse, M.; Johne, S. Ibid, 1978, 61, 2646-2671.

9. Ephedradine A and Orantine, although isolated from different sources, are identical.

10. Sarfati, R.; Pais, M.; Jarreau, F.X. Bull. Soc. Chim. Fr. , 1971, 255-263.

11. Jacobson, R.M.; Raths, R.A. J.Org. Chem. , 1979, 44,4013

12. (a) Harada, K.; Matsumoto, K. J. Org.Chem., 1966,31,2985

(b) Liwschitz, Y.; Singerman, A. J. Chem. Soc.,C 1966, 1200.

(c) Wakabayashi, T.; Kato, Y.; Watahbe, K. Chem Lett. , 1976, 1283.

(d) Abbott, D.J.; Colonna, S.; Stirling, C.J.M.

J. Chem. Soc., PI, 1976, 492.

(e) Hansen, J.J.; Kjaer, A. Acta Chem. Scand., B , 1974, 28, 418.

(f) Nakajima, Y.; Oda, J.; Inouye, Y. Agr. Biol. Chem., 1975, 39, 2065.

(g) Furukawa, M.; Okawara, T.; Terawaki, Y. Chem. Pharm. Bull. , 1977, 25, 1319.

(h) Wakabayashi, T.; Saito, M. Tetrahedron Lett., 1977, 93.

(i) Wakabayashi, T.; Kato,Y. Ibid. , 1977, 1235.

13. Achiwa, K.; Suga, T. Tetrahedron Lett. , 1978, 1119.

14. (a) Mukaiyama, T.; Takeda, T.; Fujimoto, K. Bull. Chem. Soc. Jap., 1978, 51, 3368.

(b) Meyers, A.I.,; Smith, R.K., Whitten, C.E. J. Org. Chem. , 1979, 44, 2250.

(c) Meyers, A.I.; Smith, R.K. Tetrahedron Lett, 1979 , 2749.

(d) Hashimoto, S.; Yamada, S.; Koga, K. Chem. Pharm. Bull. , 1979, 27, 771.

(e) Hashimoto, S.; Kogen, H.; Tomioka, K.; Koga, K. Tetrahedron Lett. , 1979, 3009.

15. Slosse, P.; Hootele, C. Tetrahedron Lett., 1979, 4587.

16. (a) Pluim, H.; Wynberg, H. Tetrahedron Lett., 1251; and references cited there in.

(b) Trost, B.M.; Shuey, C.D.; DiNinno, Jr., F.;McElvain, S.S. J. Am. Chem. Soc. , 1979, 101, 1284.

(c) Langström, B.; Bergson, G. Acta Chem. Scand., 1973, 27, 3118.

(e) Kretchmer, R.A. J Org. Chem. , 1972, 37, 2744.

(f) Takeda, A.; Sakai, T.; Shinohara, S.; Tsuboi, S. Bull. Chem. Soc, Jap. , 1976, 50, 1133.

(g) Yamaguchi, K.; Minoura, Y. Chem. Ind. (London), 1975, 479.

17. (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. Tetrahedron Lett. , 1975, 1707.

(b) Nakamura, A.; Konishi, A.; Tsujitani, R.; Kudo,M.; Otsuka, S. J. Am. Chem. Soc., 1978, 100, 3449.

18. Taber, D.F.; Salem, S.A.; Korsmeyer, R.W. "Abtracts of Papers", Second Chemical Congress of the North American Continent, Aug. 1980; American Chemical Society; Washington, D.C., 1980; ORG 195.

19. Danishefshy, S. Accts. Chem. Res., 1979, 12, 66.

20. Leiffler, J.E. J. Org. Chem. , 1951, 16, 1785.

PROPOSITION IV

Experiments are described to define the factors which control changes in cation binding selectivity as induced by reversible chemical changes in the ligand remote to the ligating centers. The ligands serve as simple models for selective ion transport catalysis. A simple test for evaluating chiral ligands with regard to the complex dissociation rate is also described.

* * * * * * * * * *

High selectivity has become a central theme in the developement of practical chemical processes. One of the most widespread approaches for achieving this employs cation chelation or complexation. This versatile approach, used both in a kinetic or thermodynamic sense, accounts for examples of high regioselectivity[1] , stereoselectivity[2], and chemoselectivity[3], as well as significant rate enhancements from kinetic selectivity.[4] These successes in utilizing cation complexation rely intimately on either the selectivity in binding one particular cation over others or on the efficiency of binding relative to the rate of the desired chemical process. The importance of these control elements in stoichiometric as well as both enzymatic and non-enzymatic catalytic applications has lead us to propose a program of research directed toward understanding fundamentally the factors that control binding selectivity and

binding efficiency.

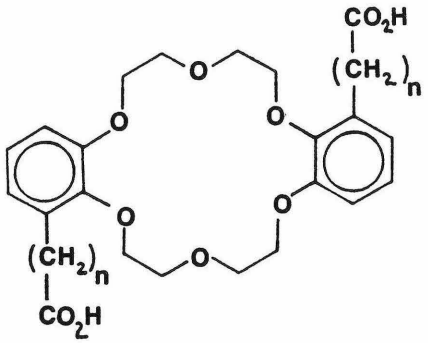
Binding Selectivity. The interest in ion transport and the ionophoric antibiotics has fostered a great deal of work toward the developement of acyclic, monocyclic and bicyclic synthetic ligands which show high binding selectivity.[5] These studies strongly implicate molecular topography as a major factor in ligand binding selectivity. Recent attempts to apply these notions to enzyme model systems which show allosteric effects have already shown limited success.[6] These studies demonstrate that complexation can mechanically induce a conformational change which measurably effects the binding selectivity in remote parts of the ligand.

We are interested in selective ion transport across a liquid membrane controlled by effects other than conformational changes. In particular, effects induced by simple reversible chemical reactions in remote parts of the ligand, yet coupled with changes in the cation binding selectivity. The binding of a particular cation is dependent on the relative association and dissociation rates (eq 1). Typically, the association rates are quite fast. Thus, metal ion selectivity should be effectively controlled by controlling the various complex-dissociation rates.

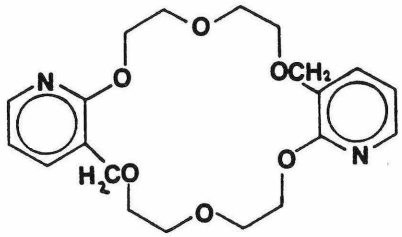
$$M^+ + L \underset{K_{dissoc}}{\overset{K_{assoc}}{\rightleftharpoons}} (ML)^+ \qquad (1)$$

Toward realizing this type of selectivity, we propose the study of ion transport from an acid phase through a liquid membrane to a basic phase as described by eq 2.[7] Ethers 1 and 2 provide simple substrates which embody the features we wish to examine as control elements for selective binding. Both ligands should be readily available using standard crown ther synthesis methodology and commercially available starting materials.[5b] Based on limited literature

precedents, each retains the feature that simple protonation or deprotonation should significantly change the binding characteristics. Ligand 1 affords a neutral complex upon



1



2

$$
\begin{array}{ccccccc}
 & M_1^+ & \underset{k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} & (M_1L) & (M_1L)^+ & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & M_1^+ \\
L + & \text{basic} & & \xleftrightarrow[\text{membrane}]{\text{liquid}} & & \text{acidic} & + L \qquad (2) \\
 & M_2^+ & \underset{k'_{-2}}{\overset{k'_2}{\rightleftharpoons}} & (M_2L) & (M_2L)^+ & \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} & M_2^+
\end{array}
$$

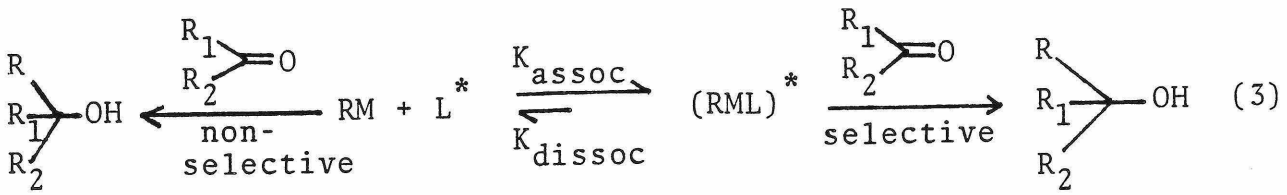
deprotonation and a charged complex under acidic conditions.[8] Ligand 2 attempts to exploit an electronic charge at a remote ligating oxygen upon protonation.[5a]

Thus the experiments (eq 2) hope to realize selective transport of one particular ion, perhaps potassium, by the protonated catalyst from an acidic solution to a basic solution and selective removal of a different cation, perhaps sodium, by the deprotonated catalyst from the basic solution

to the acidic solution. Thus, reinforcing modes of selective ion transport will be driven simply by the difference in pH of the two isolates bulk solutions. The nature of ion transport and the control factors are indeed quite complicated. It is hoped that the information gained from simple model systems such as these will aid in designing more complex and efficient catalysts.

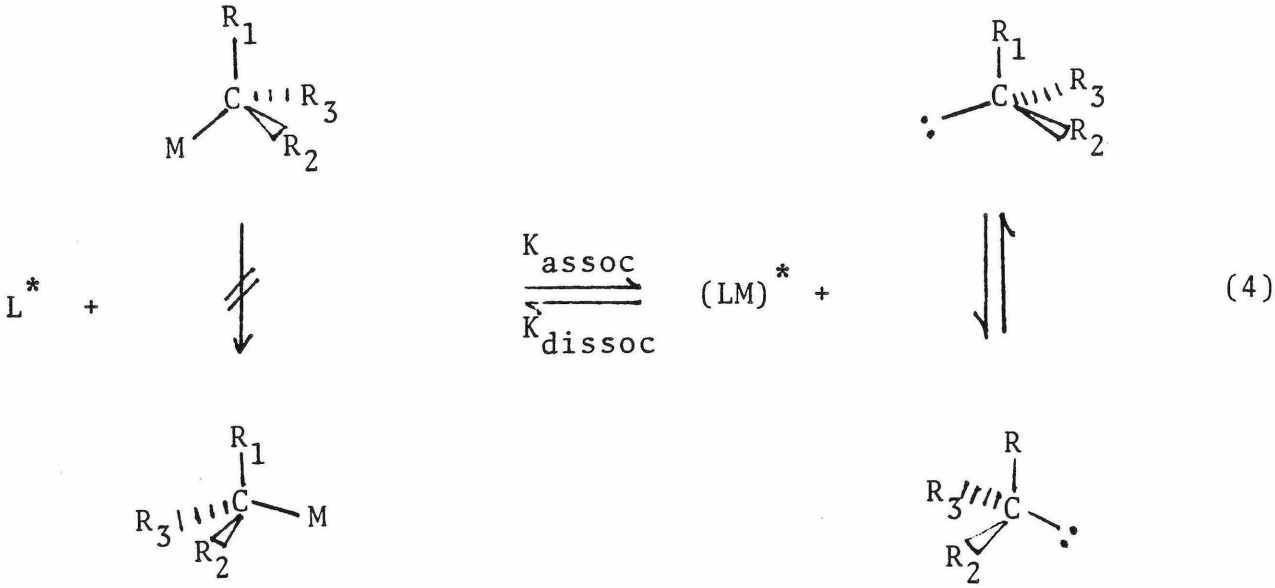
Binding Efficiency. Binding efficiency has been extensively examined. The data primarily deals with the thermodynamic stability of metal complexes although some competitive binding studies and limited kinetic data are also available. We are interested in the lifetime of certain metal complexes relative to a subsequent reaction of that complex. That is to say not just the thermodynamic stability, which reflects the difference in association and dissociation rates, but rather the magnitude of the dissociation rate relative to the rate of a subsequent chemical reaction. The problem is illustrated by the enantioselective reaction of an organometallic reagent with a ketone or aldehyde. Potentially one of the most useful approaches employs a chiral ligand to complex the organometallic reagent prior to carbonyl addition. The problem involves two independent stips as illustrated in eq 3 : 1)The rate of complex dissociation relative to carbonyl addition. 2) The enantioselectivity of carbonyl addition. Present approaches to this

problem consider only the thermodynamics of complexation and the analysis of the final product.



(3)

We would like to propose a simple test for evaluating, at least in a relative sense, the efficiency of a chiral catalyst for the conplexation step. It is known that depending on the substituents, certain organometallic (alkyllithium or grignard) reagents are configurationally stable at low temperature.[9,10] Complexation should weaken the metal-carbon bond and significantly lower the inversion barrier. Thus, as illustrated in eq 4, facile inversion at the carbanionic center of a complexed organometallic would indicate a high barrier to complex dissociation and hence a successful catalyst. Techniques for the preparation of asymmetric carbanions have recently become available.[9] We propose to



(4)

study the catalyzed inversion process which should be conveniently monitored by NMR. Systematic analysis by this technique should significantly aid in defining the important design features for efficient chiral catalysis for this and similar chemical processes.

References and Notes

(1) (a) Andrews,G.C. Ph.D. Dissertation, Univ. Calif. Los Angeles, Calf., 1974.

(b) Biellmann, J. F. ; Vicens, J.J. Tetrahedron Lett., 1978, 467-470.

(c) Chassains, G.; Lett, R.; Marquetta, A. Ibid., 1978, 471-474.

(2) (a) Still, W.C.; Schneider, J.A. Tetrahedron Lett. , 1980, 21, 1035-1038.

(b) Eliel, E.L.; Koskimies, J.K.; Lohri, B. J. Am. Chem. Soc., 1978, 100, 1614-1616.

(c) Holton, R.A., Ibid., 1977, 99, 8083-8085.

(3) (a) Mukaiyama, T.; et.al. Bull. Chem. Soc. Jap. , 1979, 52, 555.

(b) Horner, et. al. Chem. Ber. , 1970, 103, 2984.

(4) Groves, J.T.; Dias, R.M. J. Am. Chem.Soc. , 1979,101, 1033-1035.

(5) (a) Vogtle, F.; Weber, E. Angew. Chem. Int. Ed. Eng.,

(b) Gokel, G.W.; Durst, H.D. Synthesis, 1976, 168-184.

(c) Lehn, J.M. Accts. Chem. Res. , 1978, 11, 49-56.

(6) (a) Rebek, Jr.,J.; Wattley, R.V.; Costello,T.; Gadwood, R.; Marshall,L. J. Am. Chem. Soc., 1980, 102, 7398-7400.

(b) Rebek, Jr.,J.; Wattley, R.V. Ibid.,1980, 102,

4852-4854.

(c) Shinkar, S.; Shigematsu, K.; Ogawa, T.; Minami. T.; Manabe, O. Tetrahedron Lett. , 1980, 21, 4463-4466.

(7) A simple apparatus for perfoming these types of ion transport studies has been described (ref 6)

(8) (a) Helgeson, R.C.; Koga, K.; Timko, J.M.; Cram,D.J. J. Am. Chem.Soc., 1973, 95, 3021-3023.

(b) Tummler, B.; Maass, G.; Vogtle, F.; Sieger, H.; Heimann, U.; Weber, E. Ibid., 1980, 102, 2588-2598.

(9) Still, W.C.; Sreekumar, C. Ibid., 1980, 102, 1201-1202.

(10) Niemeyer, H.M. Tetrahedron , 1977, 33, 2267-2270.

PROPOSITION V.

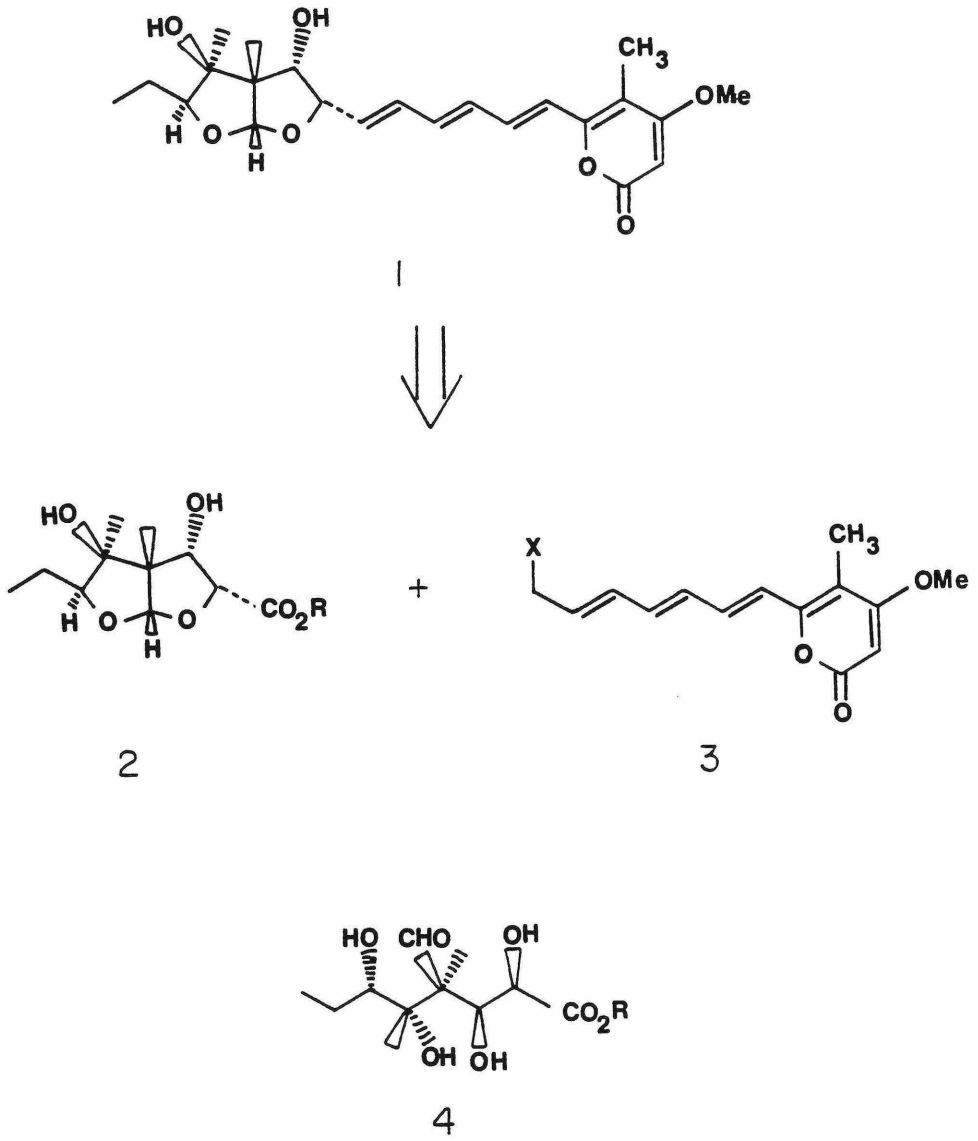
An approach to the synthesis of asteltoxin, a mycotoxin produced by Aspergillus stelatus, is described. All stereocenters are efficiently controlled relative to the C_3 carbinol.

* * * * * * *

Mycotoxins are produced by the action of certain fungi during the spoiling of foodstuffs. The widespread occurrence, acute toxicity and high carcinogenicity of this class of compounds has elicited a considerable amount of biological and pharmacological interest. The synthetic interest has been as yet relatively limited.[1,2] Herein we propose the synthesis of asteltoxin, (1), a mycotoxin recently isolated from Aspergillus stellatus.[3]

Asteltoxin,(1), possess structural features similar to the more common aflatoxins. The cis fused bis furan is unique only by virtue of the methyl group at the ring fusion. As in the aflatoxins, the ring system is highly oxygenated. Finally, the α-pyrone is reminiscent of the coumarin ring system common to the aflatoxins.

Scheme I.



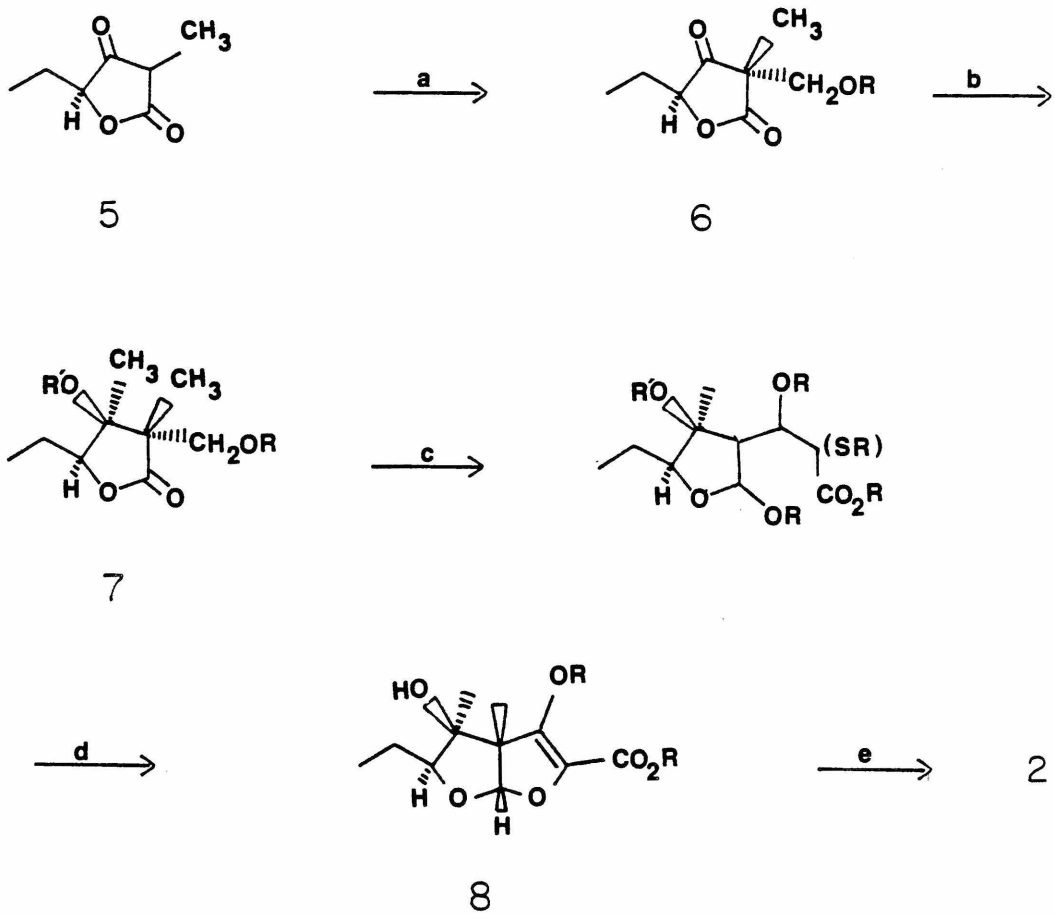
A partial retrosynthetic analysis is illustrated in Scheme I. Disconnection at the Δ_{8-9} double bond leads to synthons 2 and 3. Subunit 2 embodies the six stereocenters of asteltoxin. Analysis of the deketalized form 4 shows the complexity of the stereochemical problems. The bicyclo(3.3.0) ring system should, however, ensure the cis ring fusion.

Further, the nature of the ring system should permit control of the stereochemistry at C_6 and C_7 after cyclization. The fully substituted carbons at C_4 and C_5 are then the pivotal points in the stereochemical analysis of asteltoxin. The synthesis of subunit 2 focusing on the control of stereochemistry at C_4 and C_5 is outlined in Scheme II.

Starting lactone 5 should be readily available by condensation of ethyl propionate with the corresponding α-hydroxyaldehyde followed by lactonization and oxidation. Alkylation of 5 with a chloromethylalkylether should proceed with high selectivity to give 6. Early work by Stork[4] and more recently by Robin has demonstrated high efficiency in diastereoselection induced by a stereocenter endocyclic to the reacting center such as at C_3. Two potential aberrant reaction pathways yet remain. Double deprotonation of 5 would afford a furan dianion which should be somewhat stabilized due to aromatization. The stability of similar potential furan precursors in the prosence of stabilized carbanions suggests aromatization should not be a problem.[6] More serious is the question of C- vs. O- alkylation. This has been addressed in a number of amibident systems,and conditions which generally favor C-alkylation have been defined.[7]

Addition of methyl grignard to keto-lactone 6 should proceed with both high chemo- and stereoselectivity. Addition

Scheme II



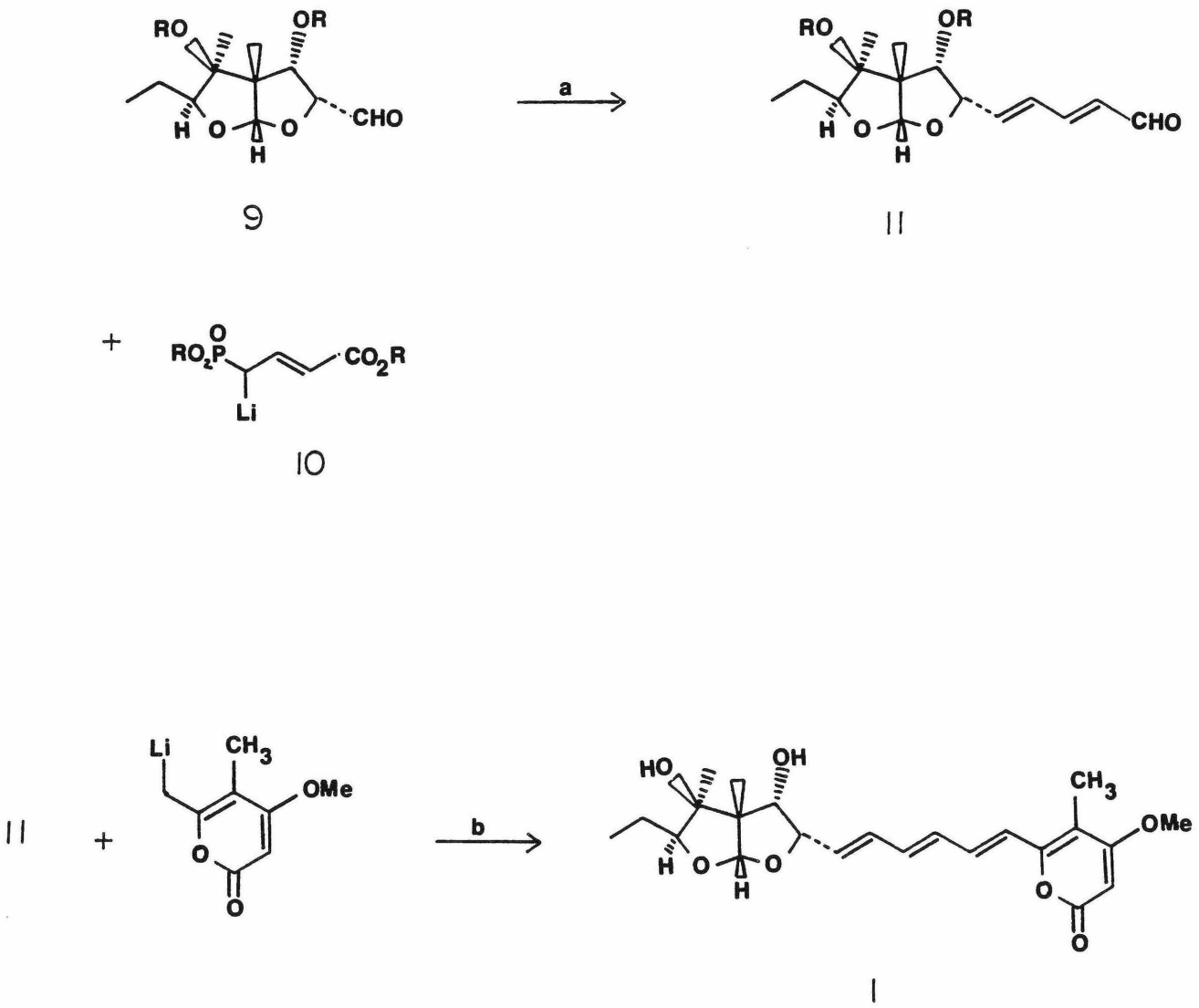
a. 1) base 2) $Me_3SiCH_2CH_2OCH_2Cl$ b. MeMgBr c.Dibal
2) MeOH/cat H^+ 3) PCC 4) $(RS)_2\bar{C}CO_2CH_3$
5) R_3SiCl d. cat H^+ e. H_2

to the ketone carbonyl is favored both on electronic grounds and due to the least hindered steric approach.[8] This latter effect should also induce the proper stereochemistry at C_4 relative to C_3. These types of 1,2 diastereoselection are well known and one might reasonably expect nucleophilic addition to keto-lactone 6 to show higher induction than the more conformationally mobile cyclopentanone derivative.[9] One potential problem involves base catalyzed fragmentation[10] of 7, but this reaction usually requires somewhat elevated temperatures. It is desirable to avoid protection of the C_4 tertiary hydroxyl due to the steric hindrance at that position.

Deprotection, elaboration of the hydroxy-methyl side chain, half-reduction of the lactone, and cyclization should give dihydrofuran 8. Hydrogenation from the least sterically encumbered β-face[11] should afford subunit 2.

Completion of the synthesis is illustrated in Scheme III. Wittig olefination and conversion of the ester to an aldehyde affords 11. Addtion of the α-pyrone anion 12 followed by elimination completes the synthesis. The α-pyrone should be readily available by cyclization of the corresponding 1,3,5 tricarbonyl derivative in acidic methanol.[12]

Scheme III



a. 1. LAH 2. MnO_2 b.MgCl/base

References and Notes

1. Schuda, P.F. "Topics in Current Chemistry", 91, Spinger-Verlag: New York, 1980, p.75.
2. Steyn, P.S. Pure and Applied Chem., 1979, 52, 189-204.
3. Krugen, G.J.; Steyn, P.S.; Vleggaar, R. J. Chem. Soc., Chem Commun, 1979,441
4. Stork,G.; Clarke, Jr., F.H. J. Am. Chem Soc., 1961, 83, 3114-3125.
5. (a) Robin, J.P.; Gringore, O.; Brown, E. Tetrahedron Lett., 1980, 21, 2709-2712.
   (b) see also: Schöllkopf, U.; Hausberg, H.H.; Hoppe, I.; Segal, M.; Reiter, U. Angew Chem. Int. Ed., 1978, 17, 117-119.
6. Herrmann, J.L.; Berger, M.H.; Schlessiger, R.H. J. Am. Chem. Soc., 1973, 95, 7923.
7. (a) Singh, J. J. Org. Chem., 1980, 45, 3368-3369.
   (b) Barlo, A.; Benetti, S.; Pollini, G.P. Synthesis , 1973, 316.
   (c) Taylor, E.C.; Hawks,III,G.H.; McKillop, A. J. Am. Chem. Soc., 1968, 90, 2421-2422.
8. Kayser, M.M.; Morand, P. J. Org. Chem., 1979, 44, 1338-1340.
9. Hoffman, T.D.; Cram, D.J. J. Am. Chem Soc., 1969, 91, 1000-1008.

10. (a) Hoffman, T.D.; Cram, D.J. Ibid., 1969, 91, 1009-1020.
(b) Stowell, J.C. "Carbanions in Organic Synthesis", Wiley-Interscience: New York, 1979, p.205-208.

11. (a) Achmad, S.A.; Cavill, G.W.K. Aust. J. Chem., 1965, 18, 1989-1996.
(b) Welch, S.C.; Chayabunjonglerd, S. J. Am. Chem. Soc., 1979, 101, 6768-6769.

12. The 1,3,5 tricarbonyl compound should be readily available by quenching the dianion of 3-methyl acetylacetonate with CO_2.